Master Module
Proteinbiochemistry and Bioinformatics
March 2022

Protein interaction networks

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Institute of Molecular Biology

Emmy Noether-Programm
DFG Deutsche Forschungsgemeinschaft

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

JG|U

Some organizational information

- Questions throughout the lecture are welcome
- I will ask questions, too!
- Happy to receive feedback on the course

Outline

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1. What are protein interactions?

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2. Methods to detect protein interactions

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3. Bioinformatic resources for protein interactions

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1. What are protein interactions?
2. Methods to detect protein interactions
3. Bioinformatic resources for protein interactions
4. Graph theoretical aspects of protein interaction networks
5. Visualizing and analyzing networks using Cytoscape

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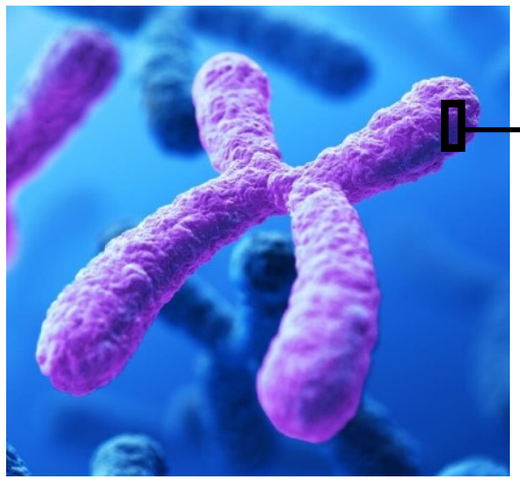
Session: Protein interaction networks

1. What are protein interactions?

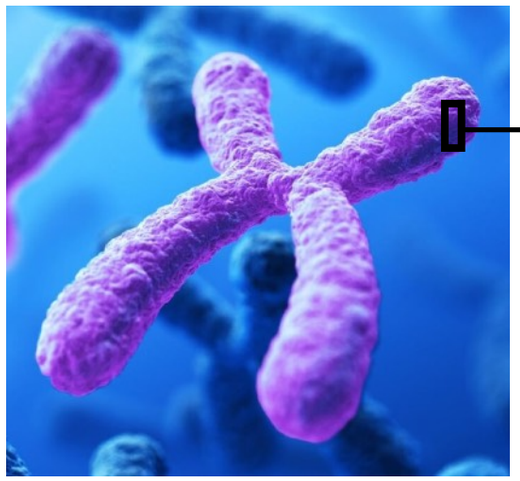
Why do protein interactions matter?



humanoriginproject.com

Gene X functions in Y - How?

Why do protein interactions matter?



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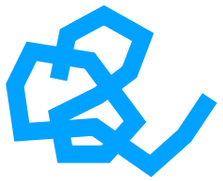

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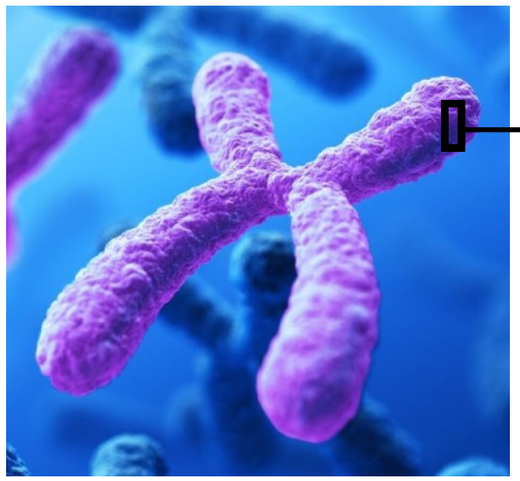

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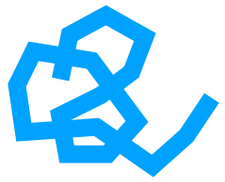

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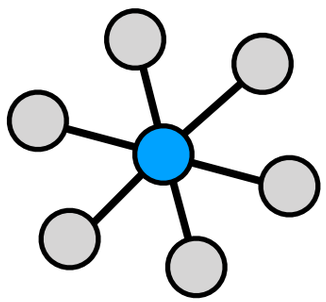
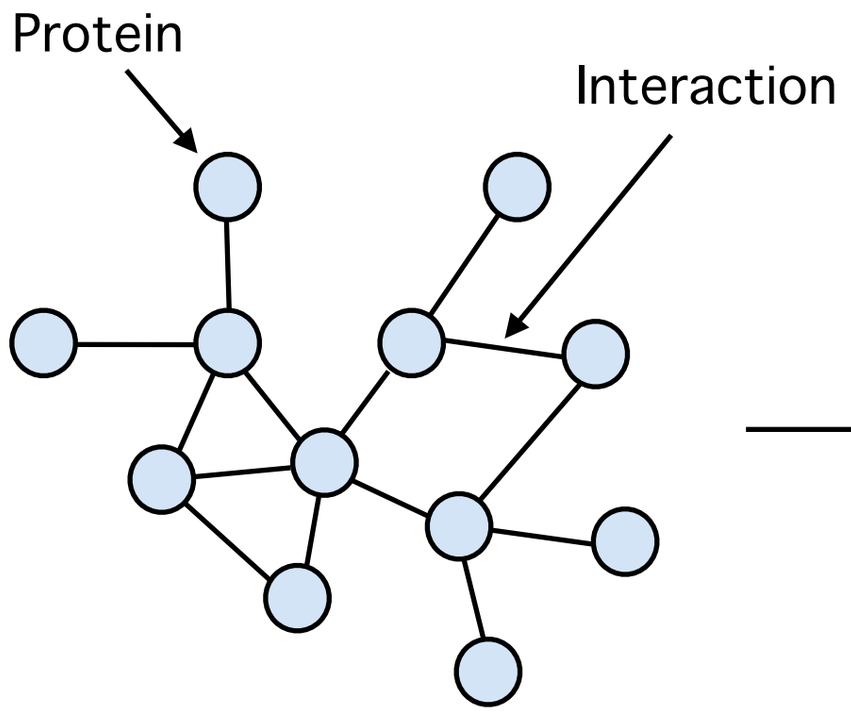


- Interactions mediate a gene's function
- Interactions inform on a gene's function

Protein interactions mediate cellular function

Genome,
Environment



Cellular function
and organization

Protein interactions mediate cellular function

Genome,
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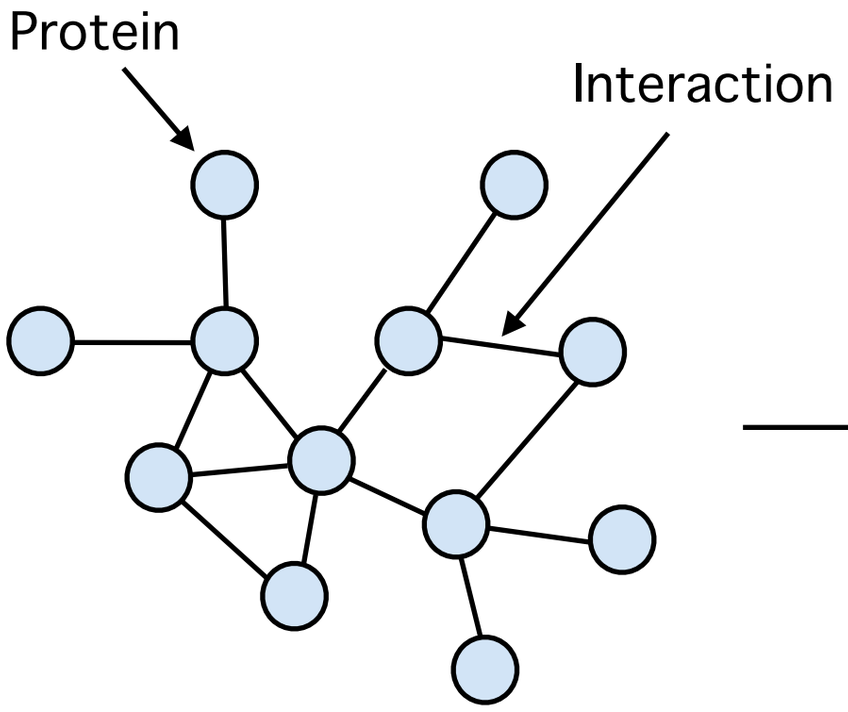
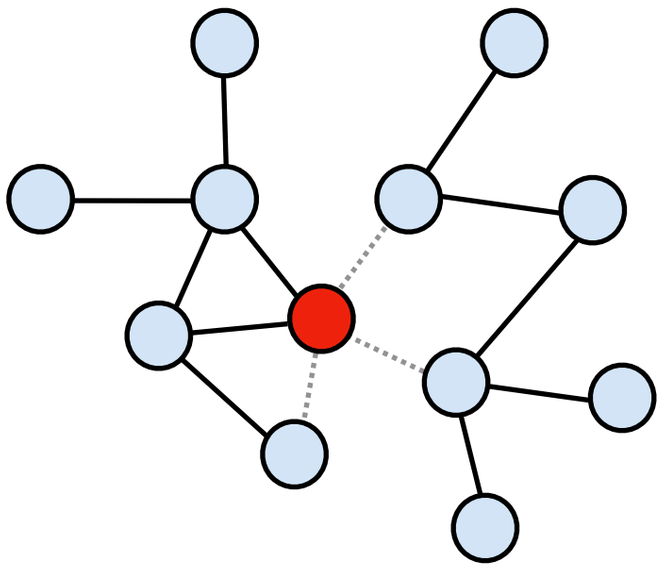


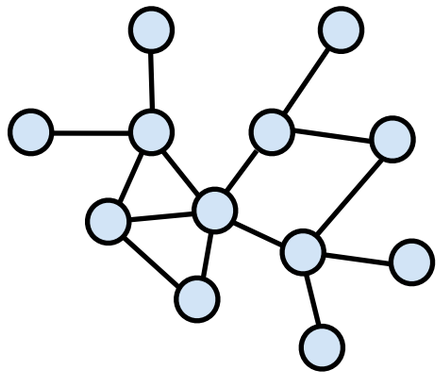
Cellular function
and organization

Mutation,
pathogen,
toxin



Disease

Protein interactions are complex



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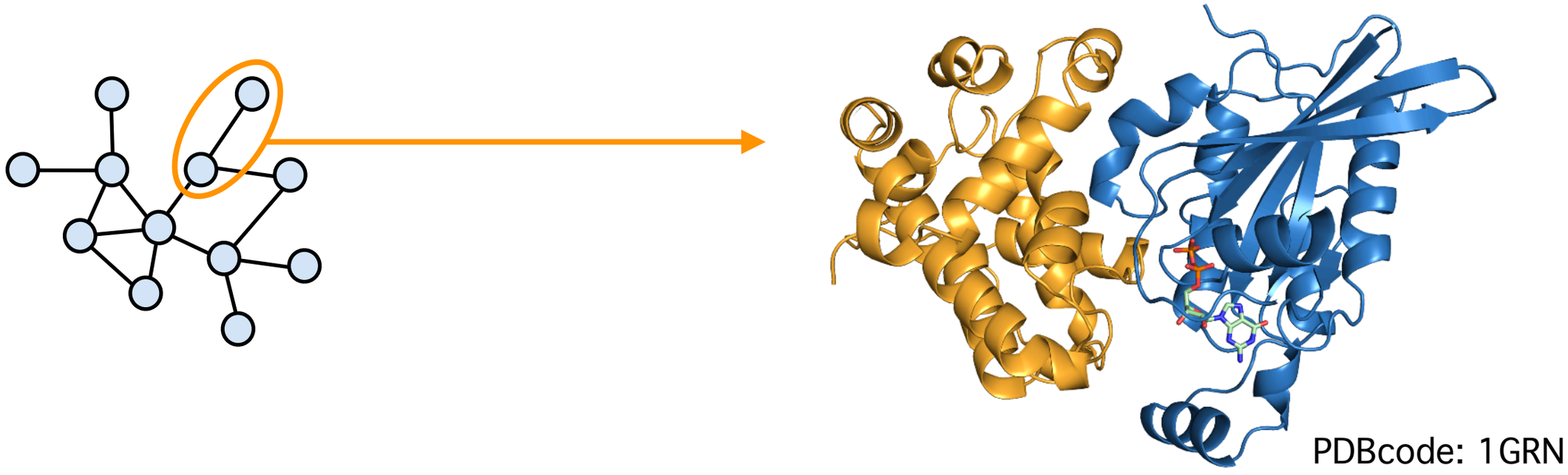

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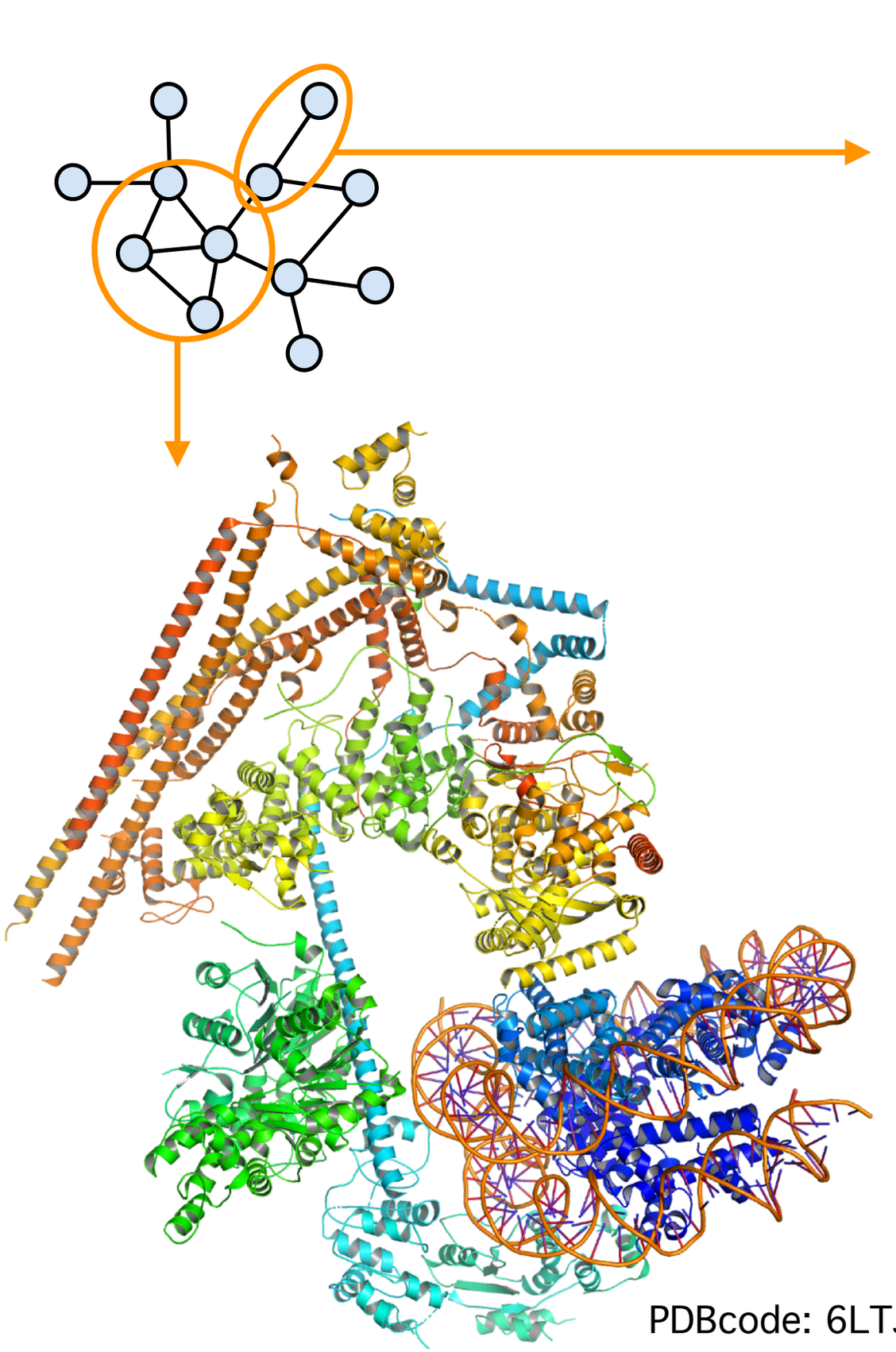
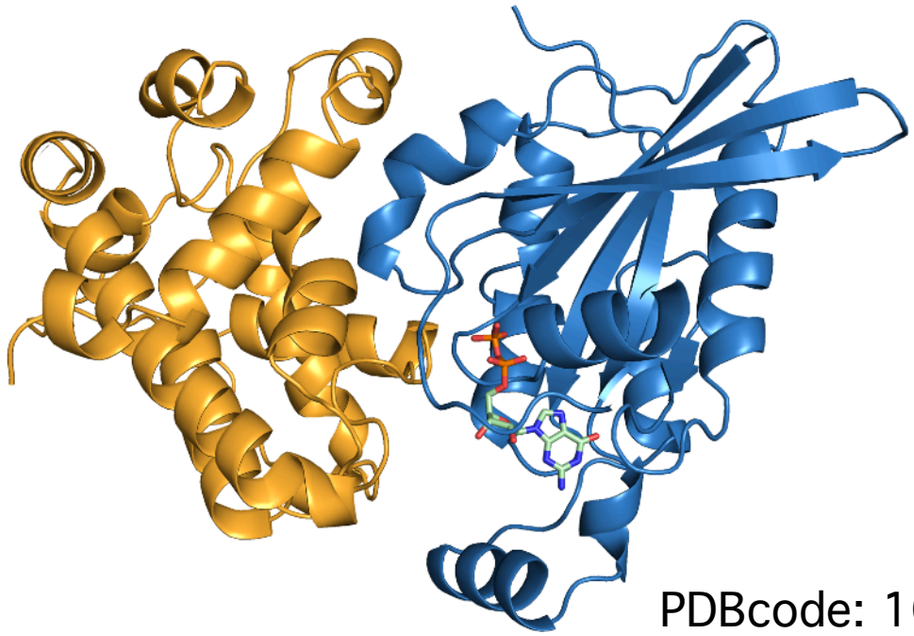
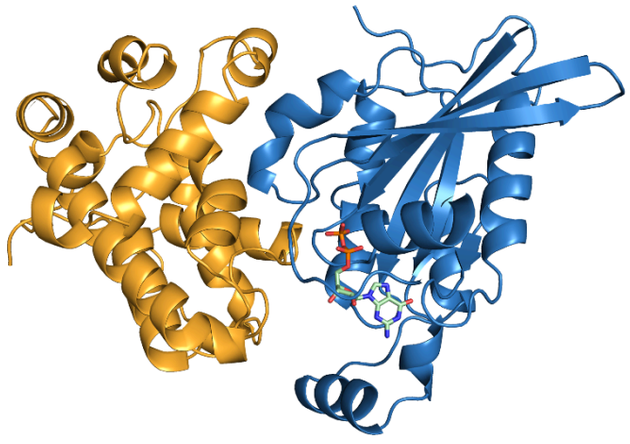


PDBcode: 6LTJ



PDBcode: 1GRN

Non-covalent contacts between amino acids mediate protein interactions



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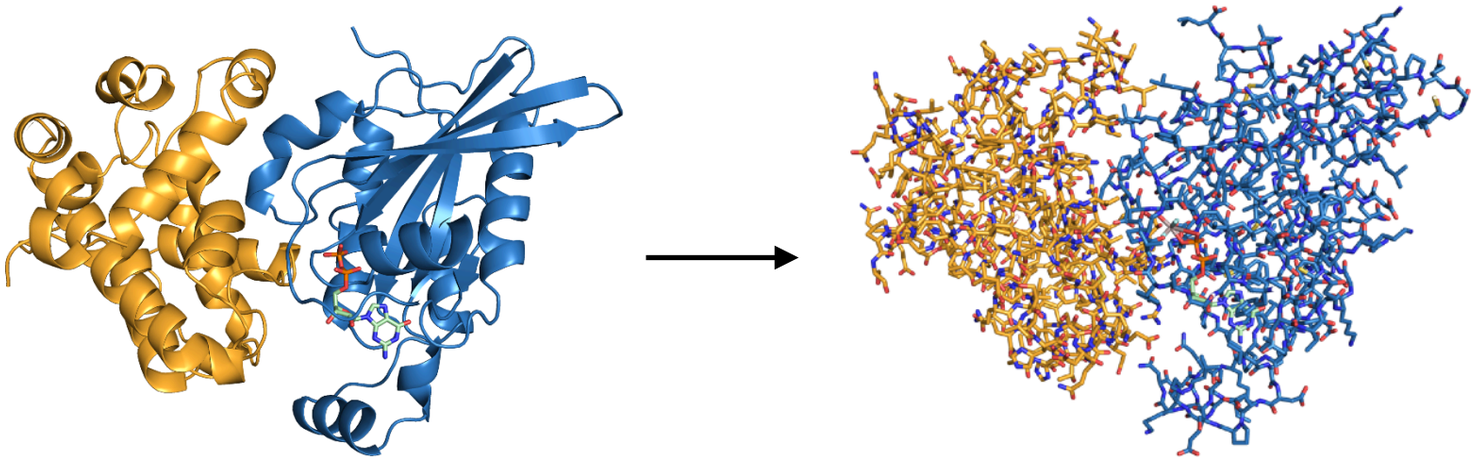

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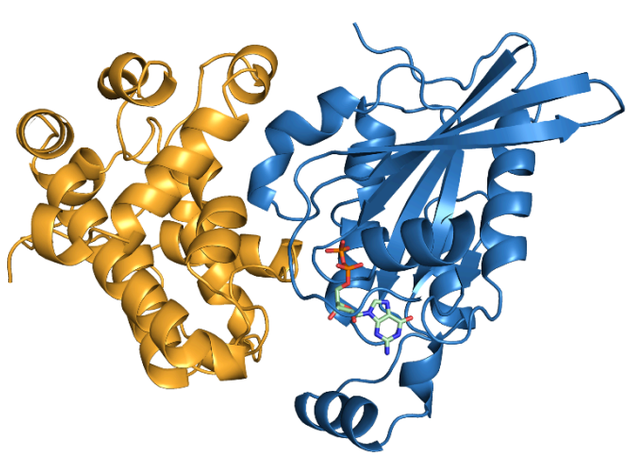
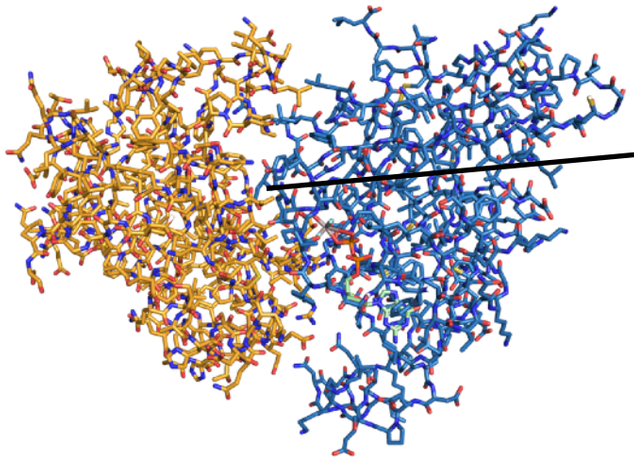
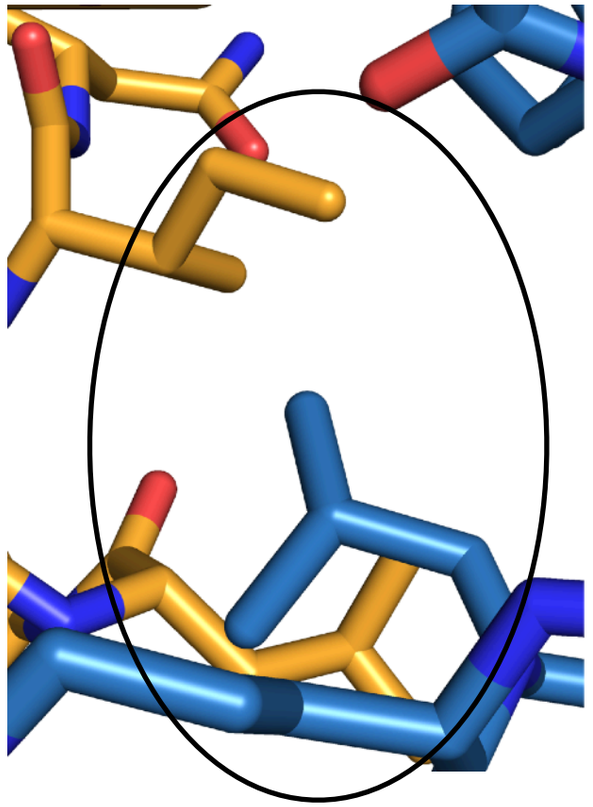




Hydrophobic contact
(van-der-Waals)



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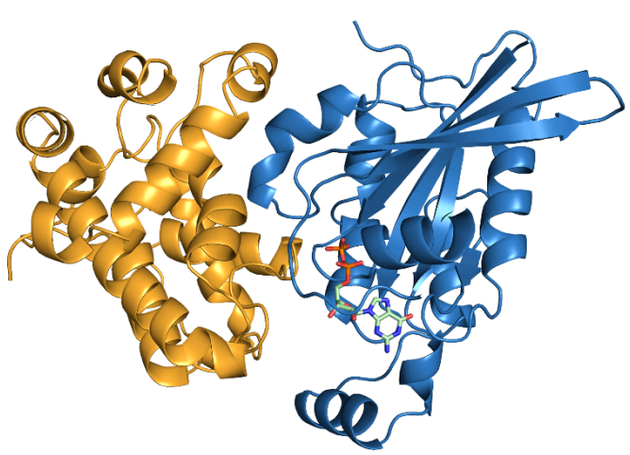

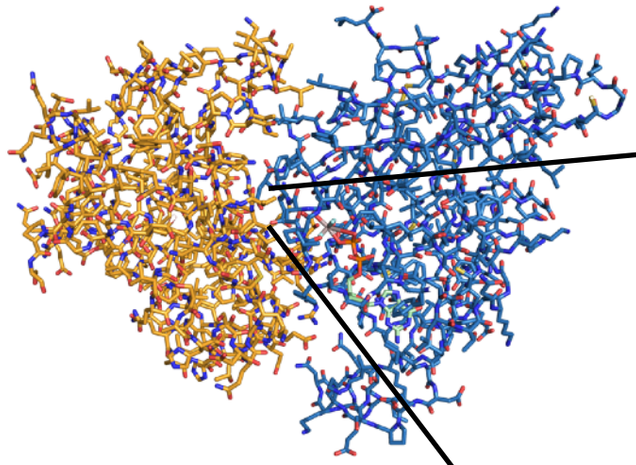

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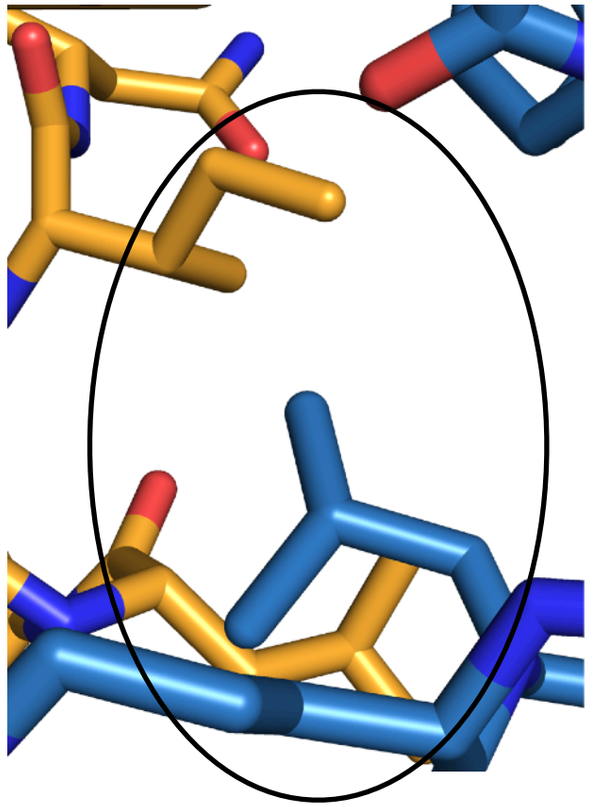

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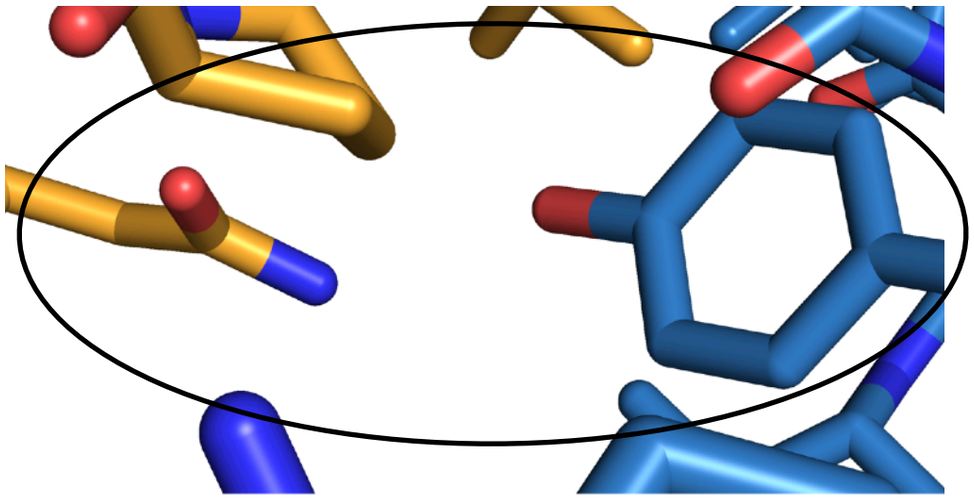

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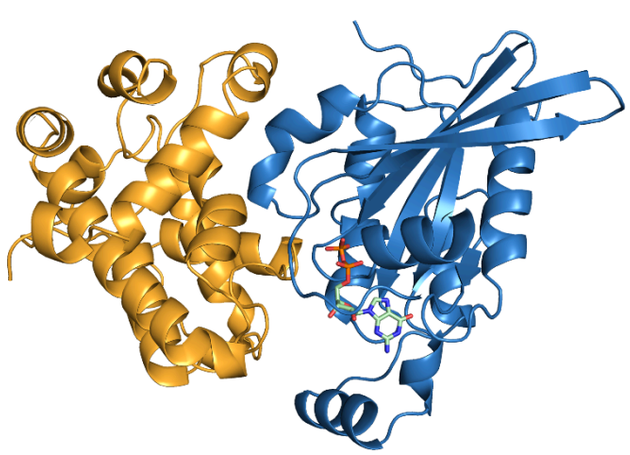

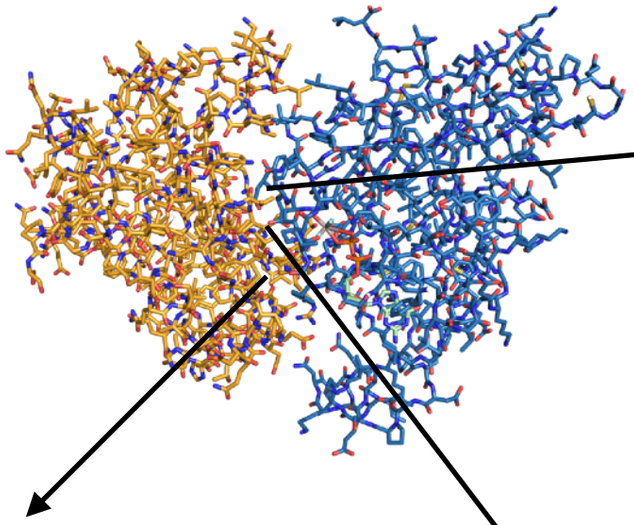

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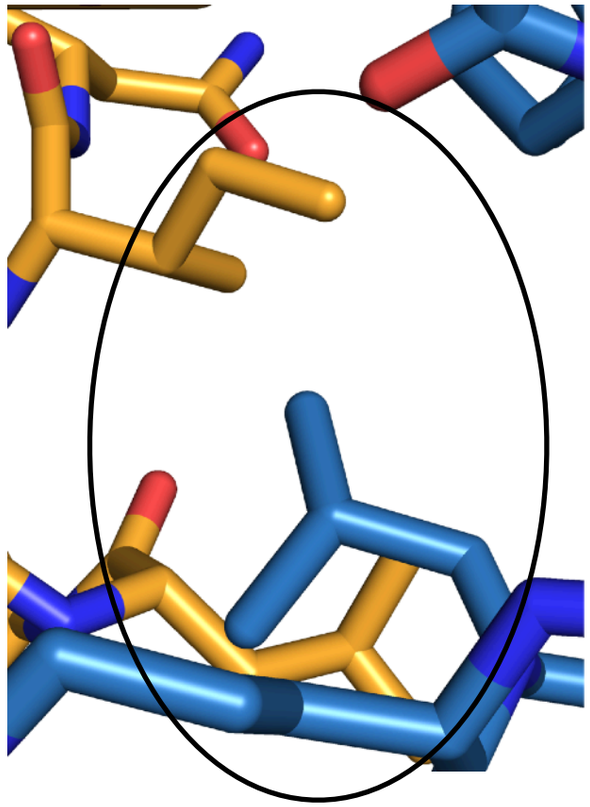
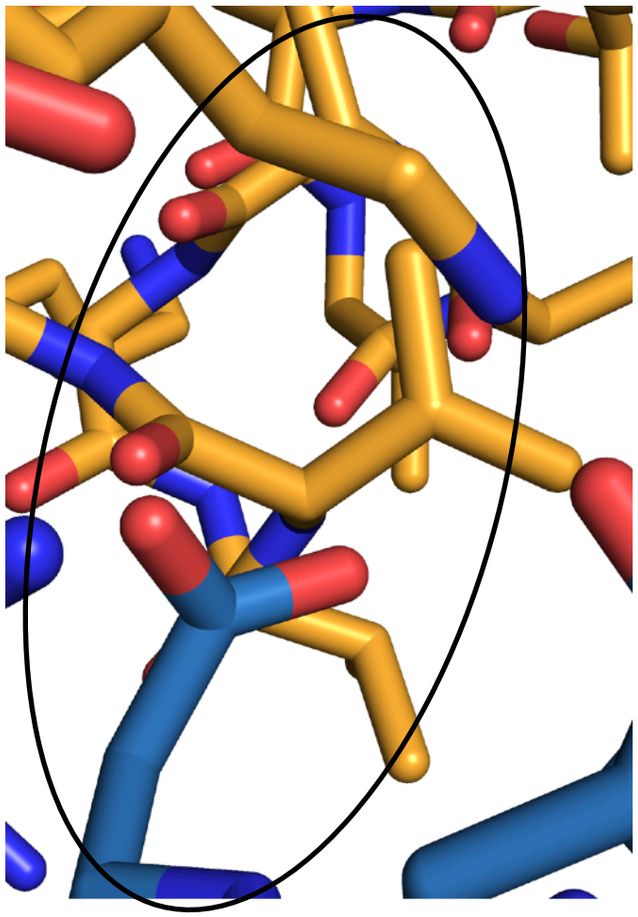


Charge contact (salt bridge)



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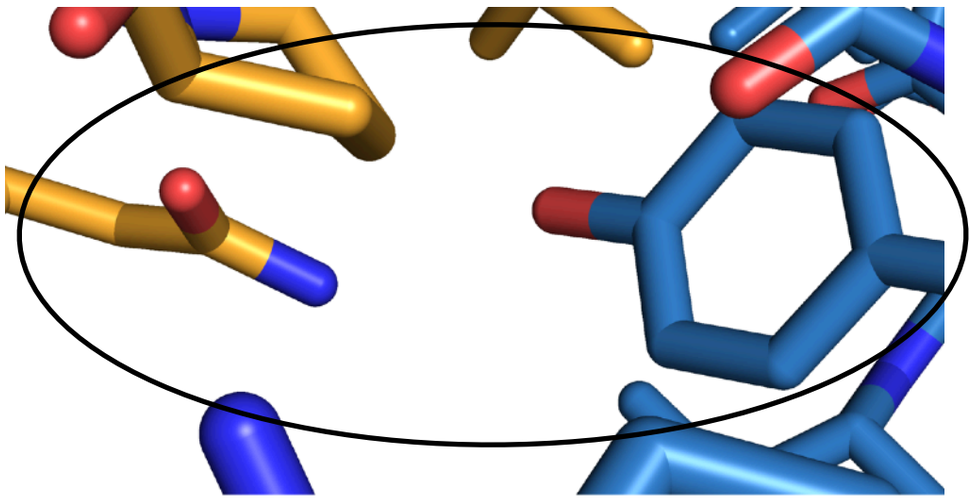

Protein interaction strength is expressed as dissociation constant K_D

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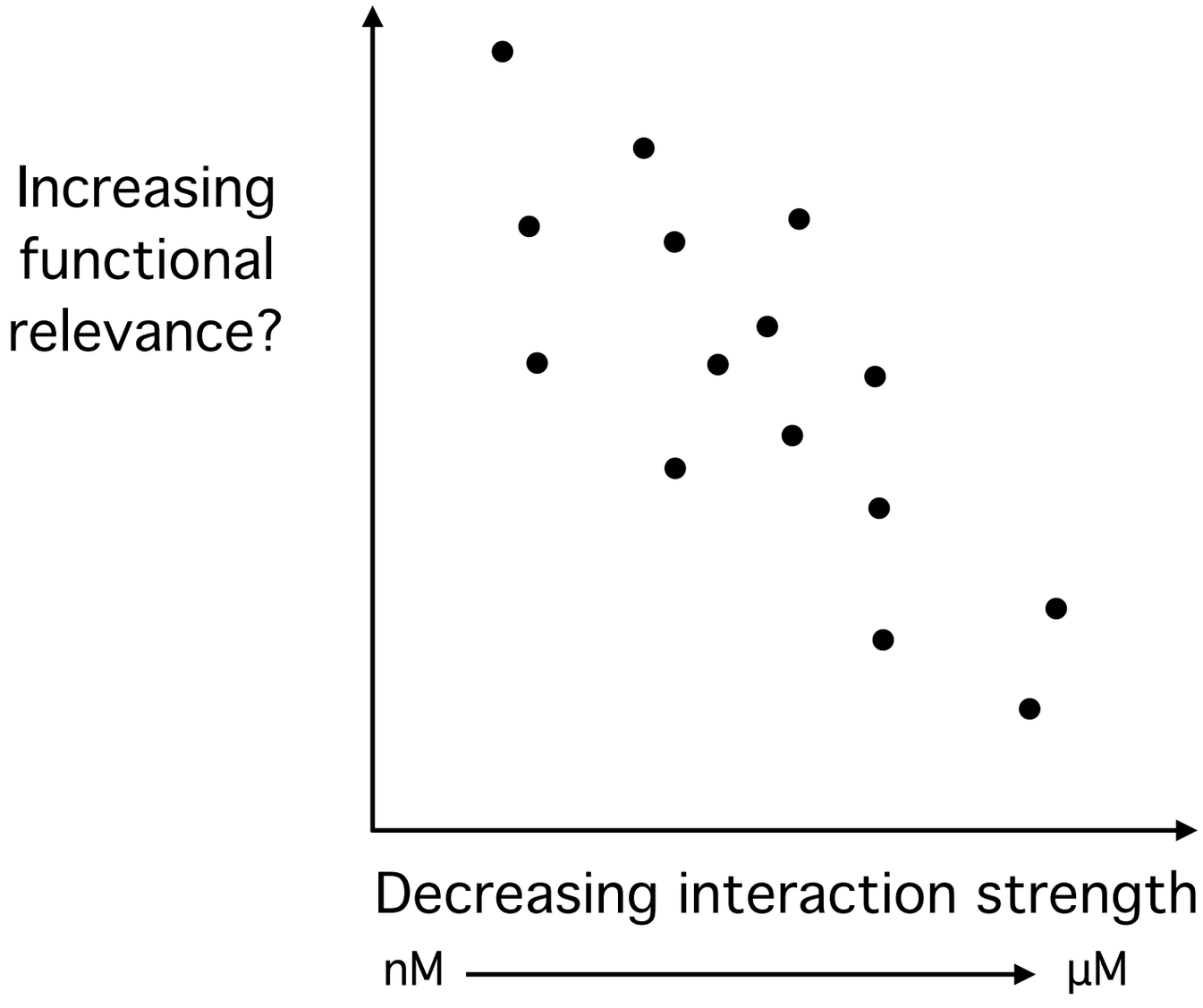

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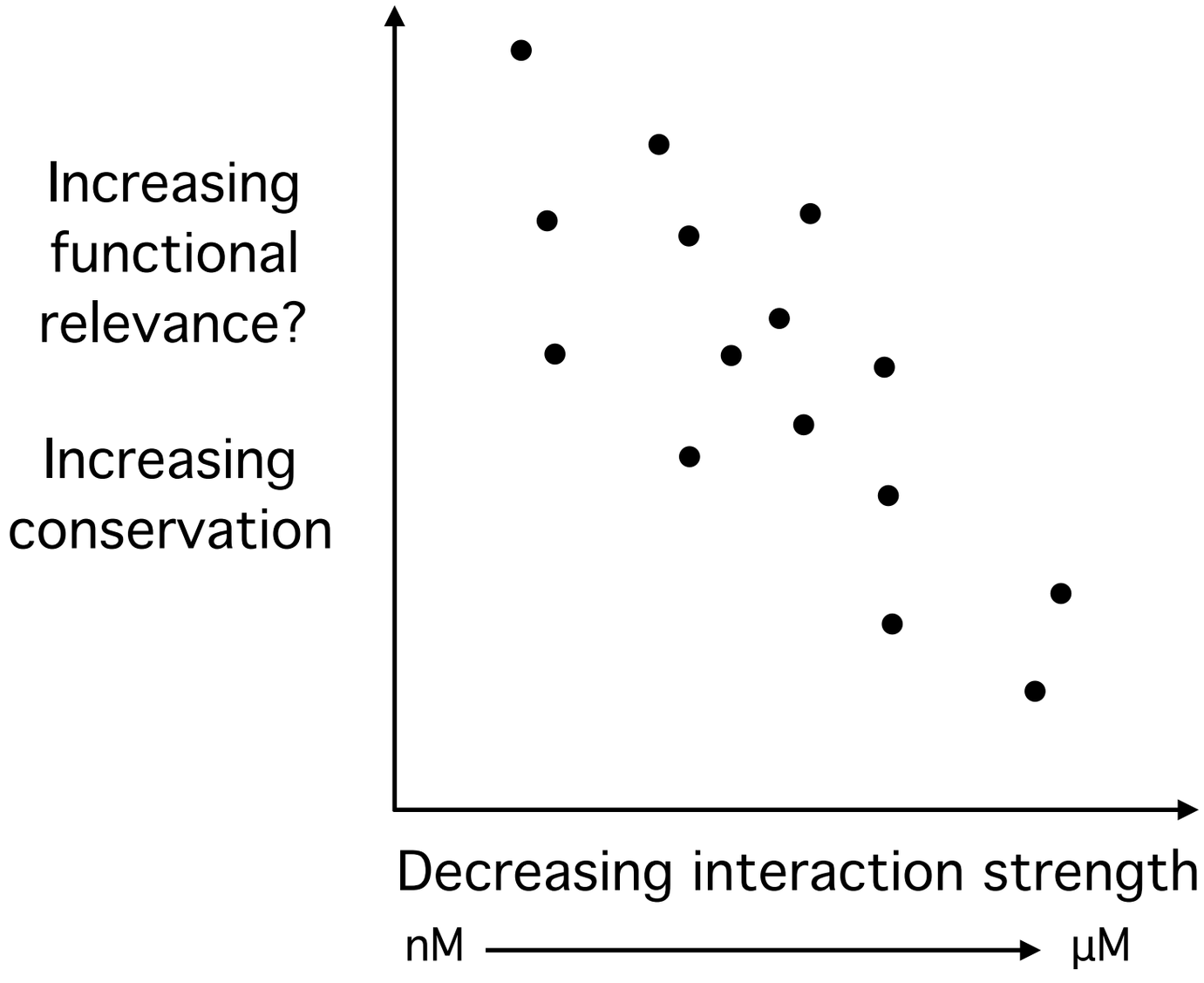

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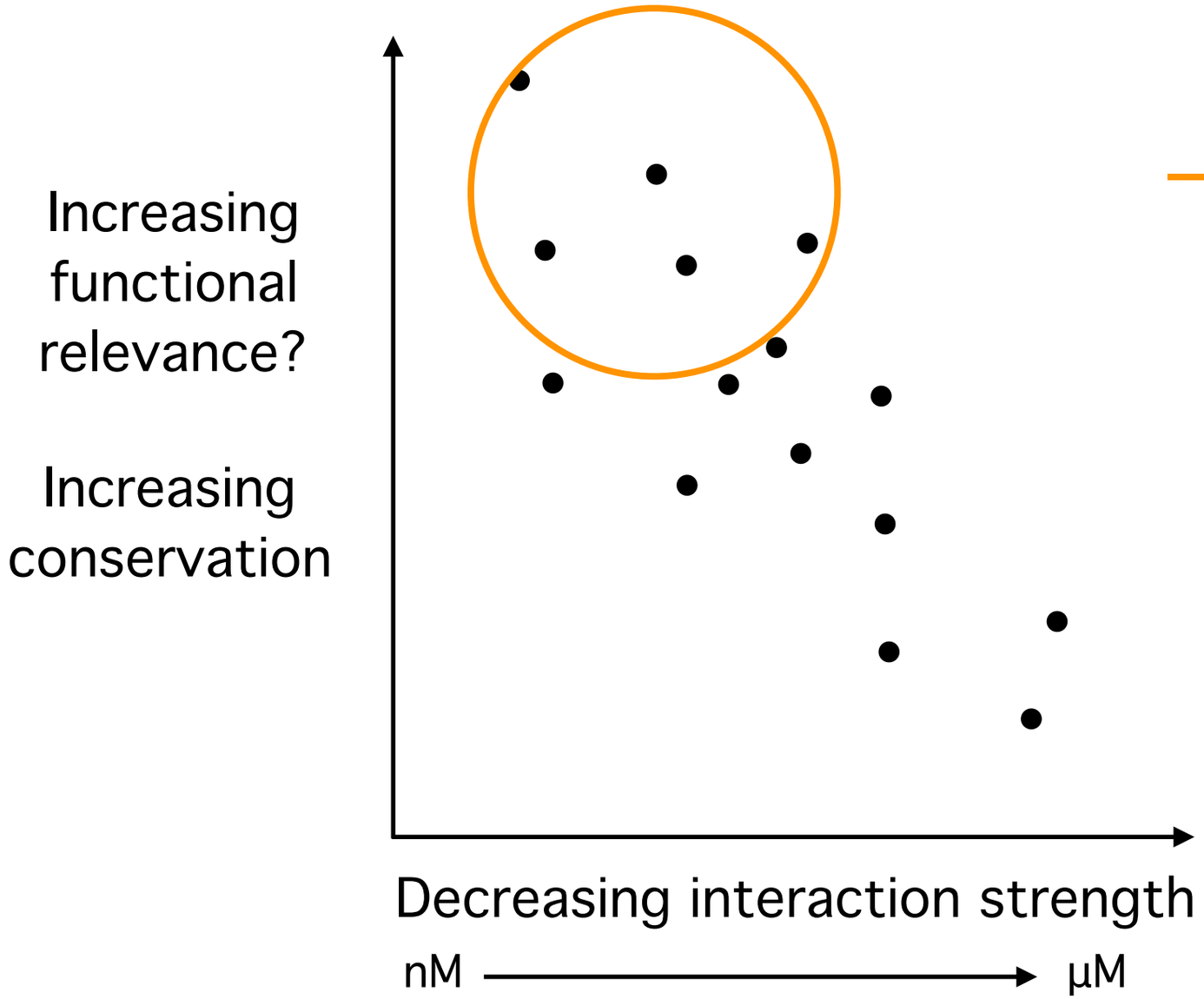

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Wan et al *Nature* 2015

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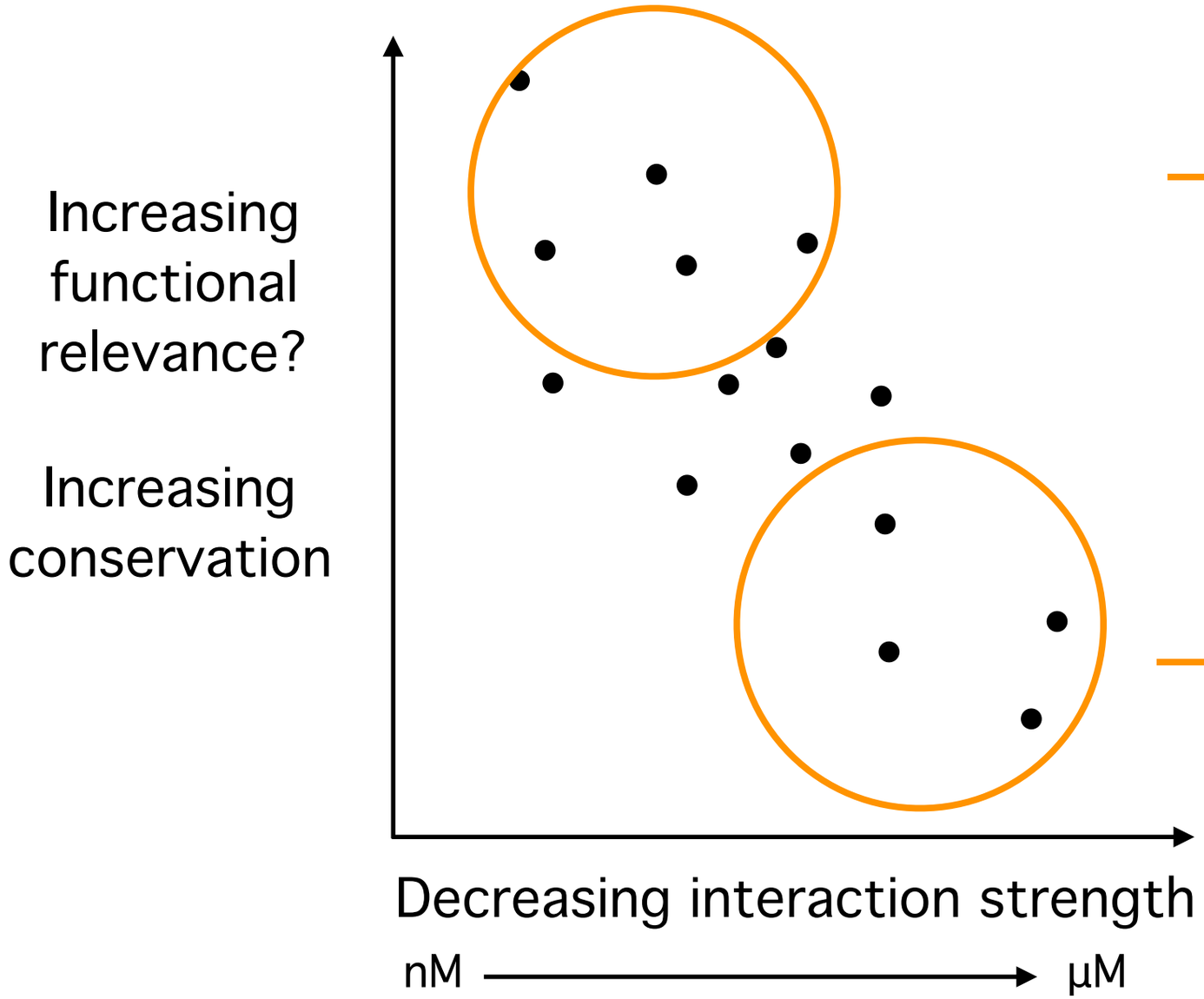

- core biological processes
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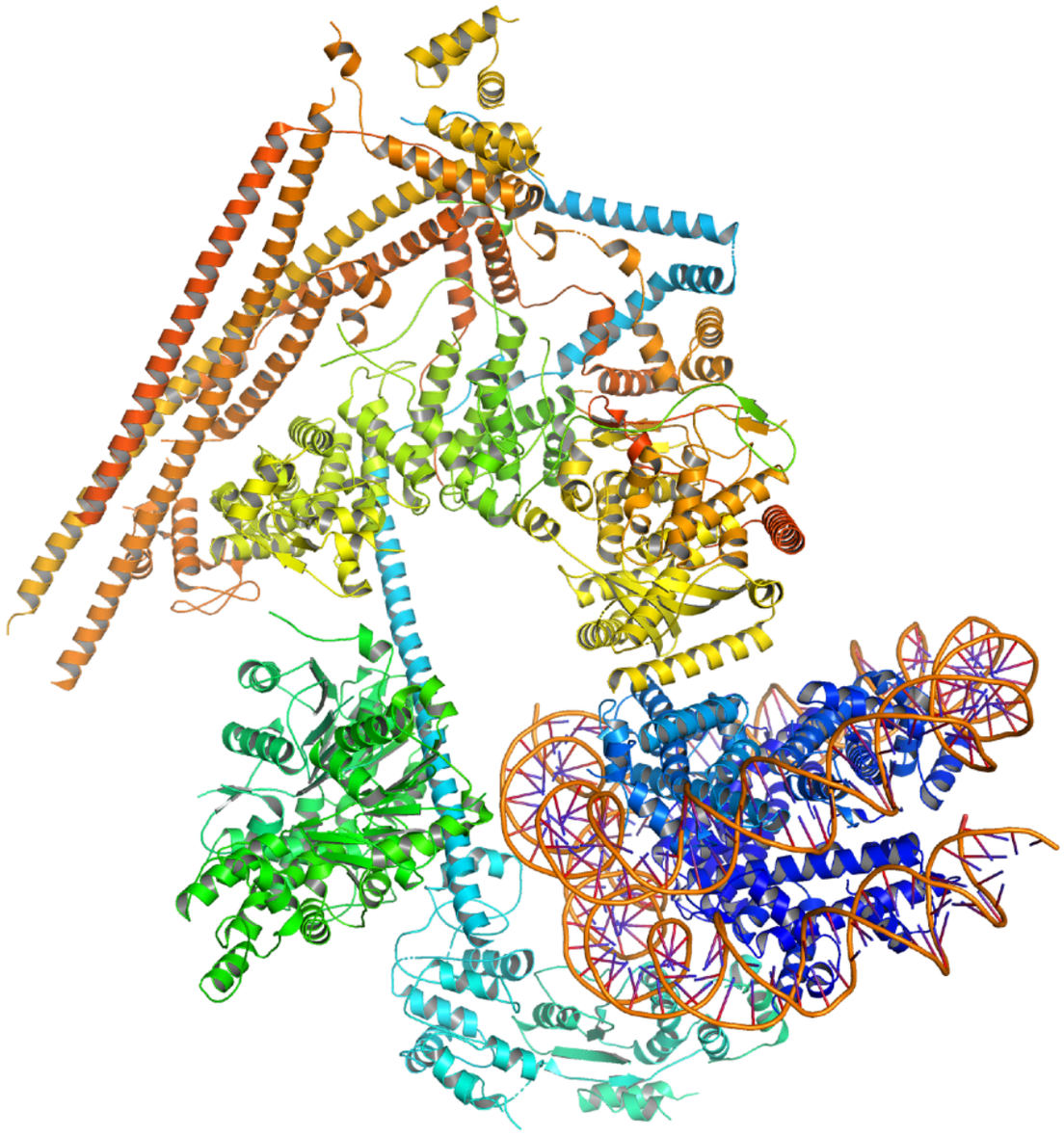
- multicellularity
- regulation, signaling

Wan et al *Nature* 2015

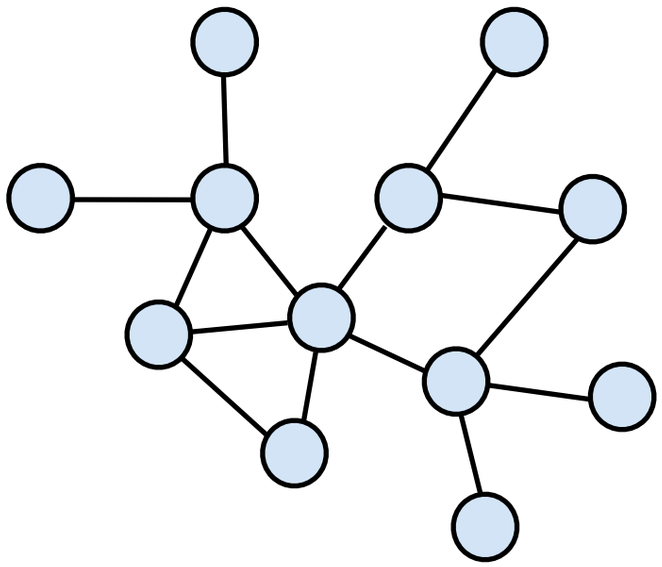
All life depends on the proper formation and dissociation of protein interactions



Mechanisms of protein interaction specificity?

If we knew all (human) protein interactions...

Complete functional annotation of all genes



Complete understanding of human biology

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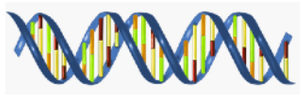
Session: Protein interaction networks

2. Methods to detect protein interactions

Why is it so hard to detect protein interactions?

Why is it so hard to detect protein interactions?

Genome

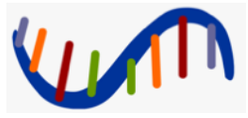


Next generation sequencing

😀

Great sensitivity

Transcriptome



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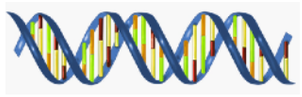

Next generation sequencing

Great sensitivity
-> Amplification via PCR

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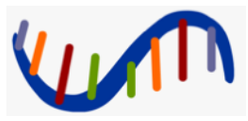

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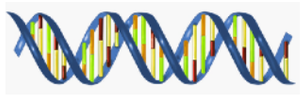

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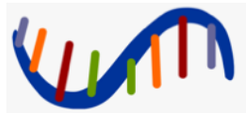

Next generation sequencing

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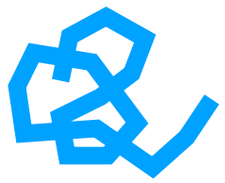
Proteome



Mass spectrometry

😕

Moderate sensitivity
-> no PCR for proteins

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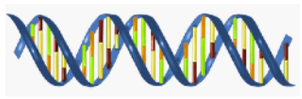

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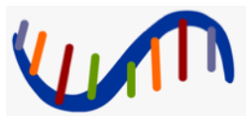

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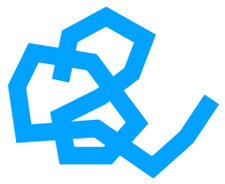

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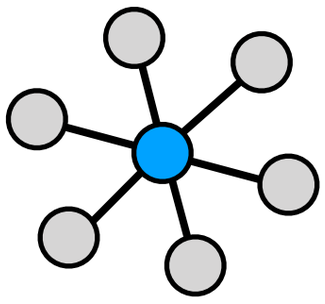
Interactome



?

- No PCR for interactions
- Interactions are a state, not a molecule

Approaches to detect protein interactions

- interaction detection method
  - experimental interaction detection
    - biochemical
      - affinity technology
      - aggregation assay
      - chromatography technology
      - cosedimentation
      - cross-linking study
      - electrophoretic mobility-based method
      - enzymatic study
      - footprinting
      - nucleotide exchange assay
      - polymerization
      - probe interaction assay
      - virotrap
    - biophysical
      - biosensor
      - circular dichroism
      - detection by mass spectrometry
      - differential scanning calorimetry
      - electron diffraction
      - electron resonance
      - enzyme-mediated activation of radical sources
      - equilibrium dialysis
      - filter trap assay
      - fluorescence technology
      - force measurement
      - force spectroscopy
      - infrared spectroscopy
      - isothermal titration calorimetry
      - light scattering
      - luminiscence technology
      - microscale thermophoresis
      - molecular sieving
      - neutron diffraction
      - neutron fiber diffraction
      - nuclear magnetic resonance
      - rheology measurement
      - scintillation proximity assay
      - small angle neutron scattering
      - thermal shift binding
      - ultraviolet-visible spectroscopy
      - x-ray crystallography
    - genetic interference
      - chemical rna modification plus base pairing prediction
      - random spore analysis
      - synthetic genetic analysis
    - imaging technique
      - atomic force microscopy
      - confocal microscopy
      - electron microscopy
      - fluorescence microscopy
      - fluorescent protein-protein interaction-visualization
      - light microscopy
      - super-resolution microscopy
      - x-ray tomography
    - phenotype-based detection assay
      - nuclear translocation assay
    - post transcriptional interference
      - antisense oligonucleotides
      - antisense rna
      - miRNA interference luciferase reporter assay
      - rna interference
    - protein complementation assay
      - Split Intein-Mediated Protein Ligation
      - adenylate cyclase complementation
      - beta galactosidase complementation
      - beta lactamase complementation
      - bimolecular fluorescence complementation
      - dihydrofolate reductase reconstruction
      - kiss
      - mammalian protein protein interaction trap
      - protein kinase A complementation
      - reverse ras recruitment system
      - split luciferase complementation
      - tox-r dimerization assay
      - transcriptional complementation assay

https://www.ebi.ac.uk/ols/ontologies/mi

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      - polymerization
      - probe interaction assay
      - virotrap
    - biophysical
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      - microscale thermophoresis
      - molecular sieving
      - neutron diffraction
      - neutron fiber diffraction
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      - rheology measurement
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      - dihydrofolate reductase reconstruction
      - kiss
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      - protein kinase A complementation
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      - split luciferase complementation
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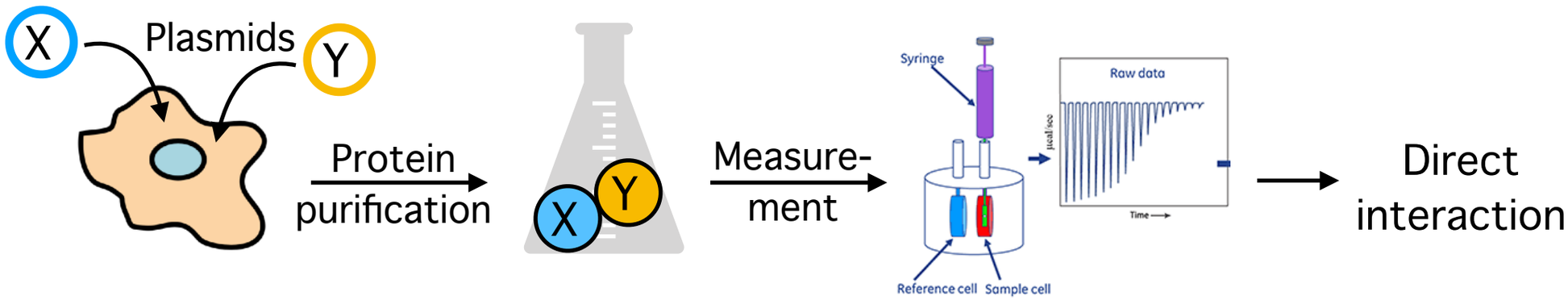
      - transcriptional complementation assay

https://www.ebi.ac.uk/ols/ontologies/mi

Detection of direct interactions



Approaches to detect protein interactions

- interaction detection method
  - experimental interaction detection
    - biochemical
      - affinity technology
      - aggregation assay
      - chromatography technology
      - cosedimentation
      - cross-linking study
      - electrophoretic mobility-based method
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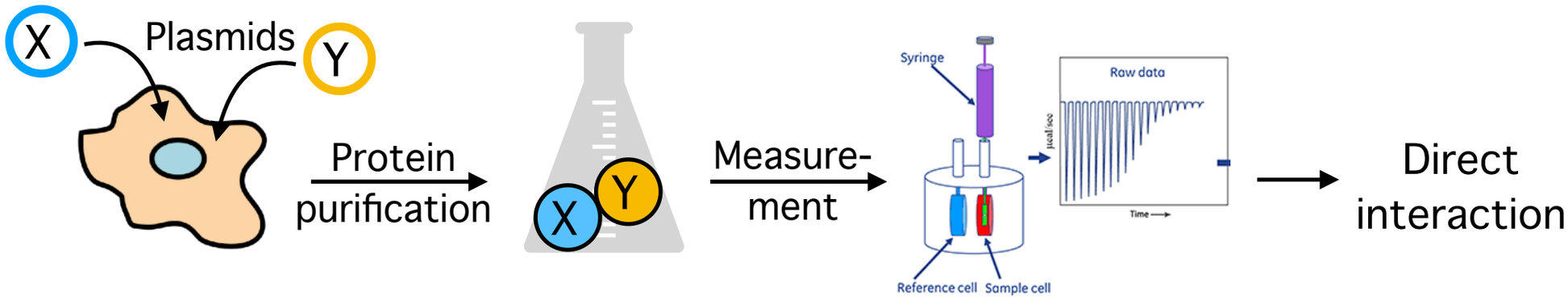
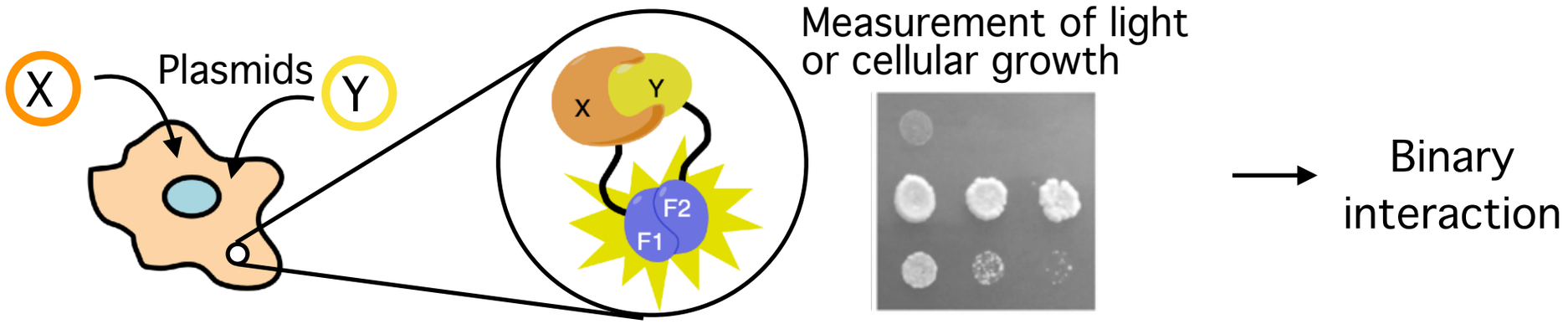


Detection of binary interactions



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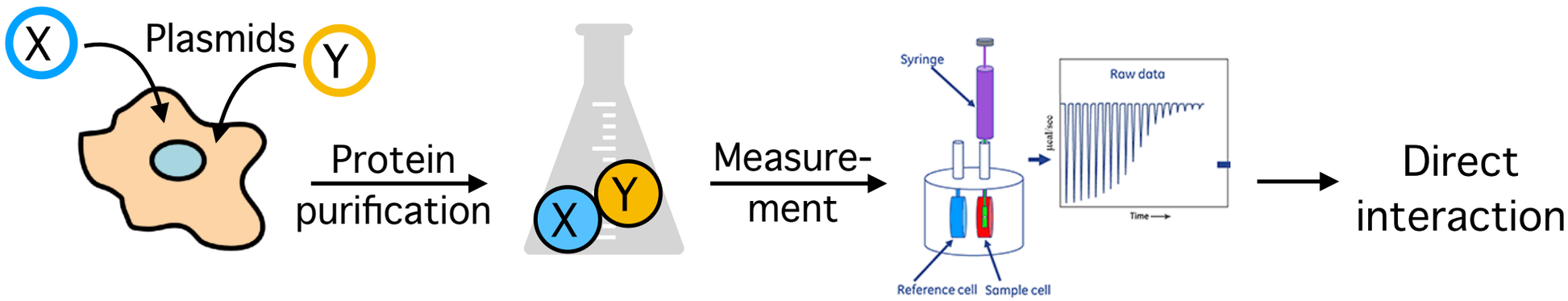

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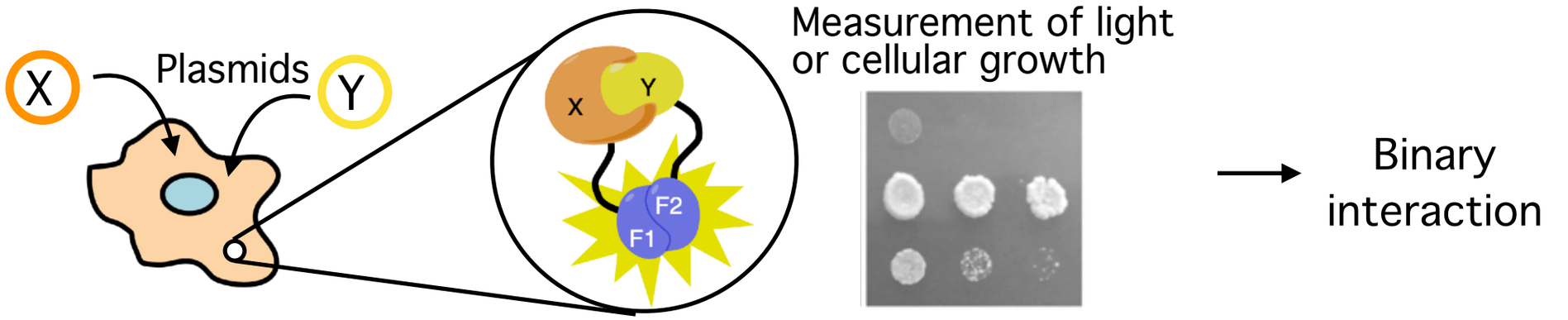
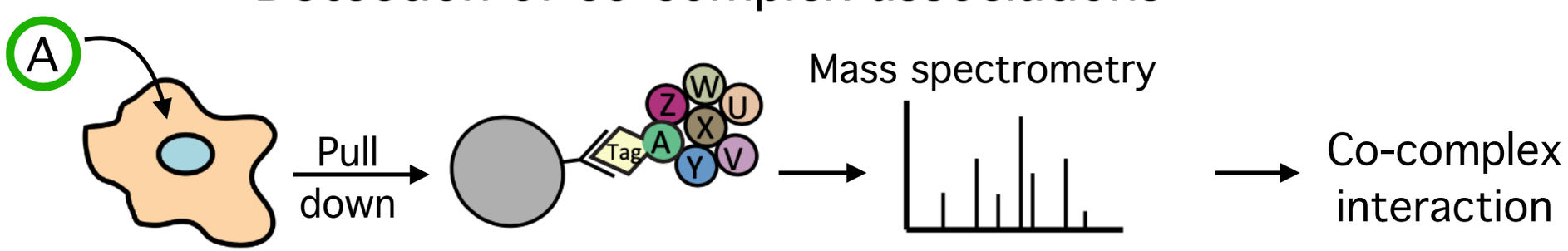


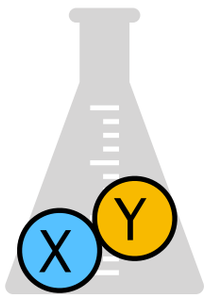
Detection of co-complex associations



Different assays produce different types of protein interaction data

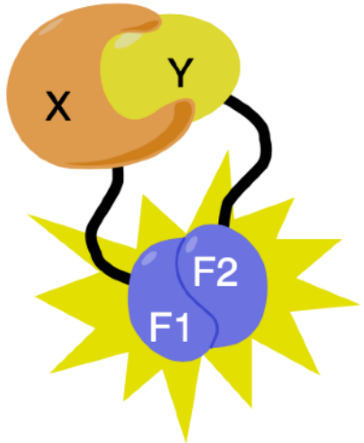
Direct assays

- direct interactions
- protein fragments
- with K_D
- low-throughput



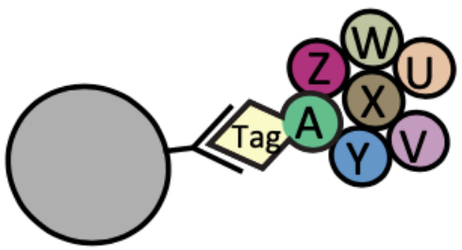
Binary assays

- binary interactions
- full length proteins
- no K_D
- over-expression



Co-complex assays

- co-complex associations
- full length proteins
- no K_D
- over-expression and endogenous



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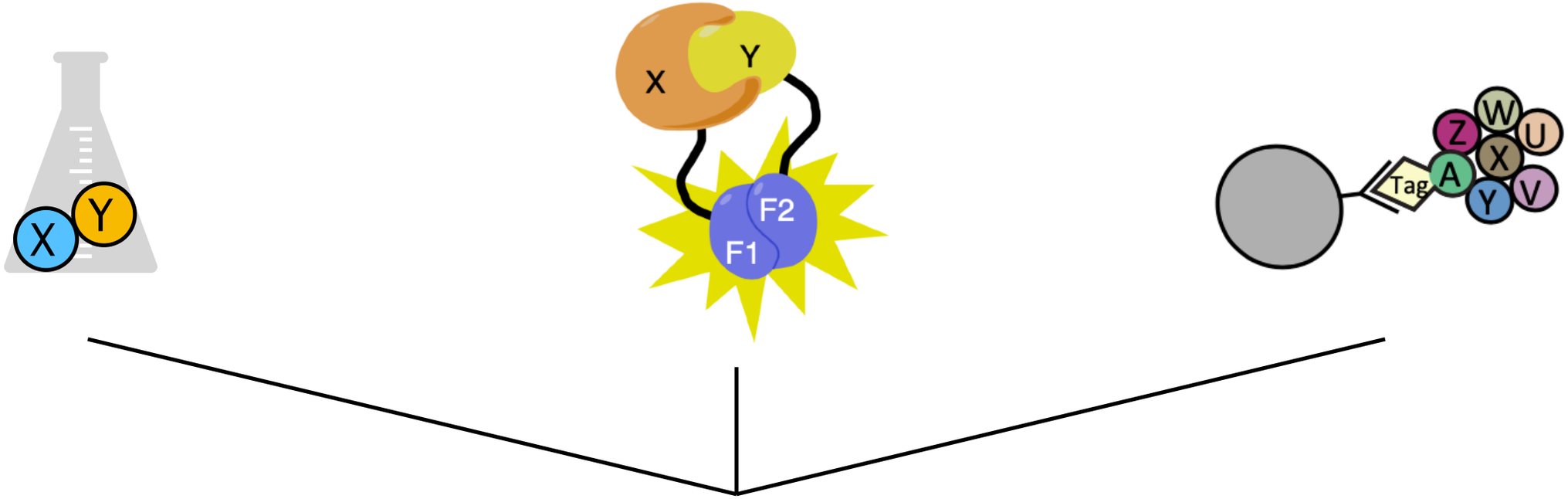

- all are called protein interactions
- assays differ in which interactions they can detect

Accuracy of protein interaction assays

Sensitivity of protein interaction assays

Braun et al *Nature Methods* 2009

Accuracy of protein interaction assays

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Why are some interactions detected by some assays and not by others?

Braun et al *Nature Methods* 2009

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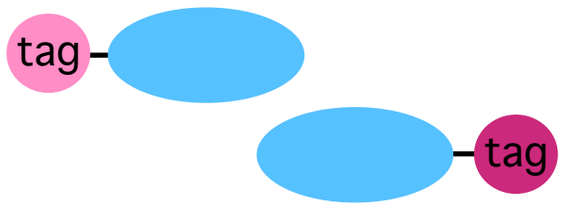
Protein fusions



Braun et al *Nature Methods* 2009

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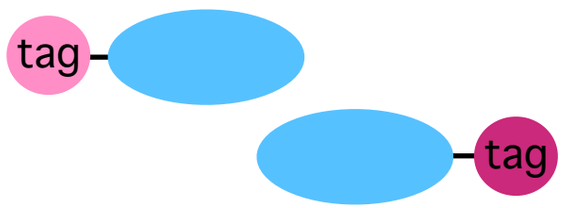
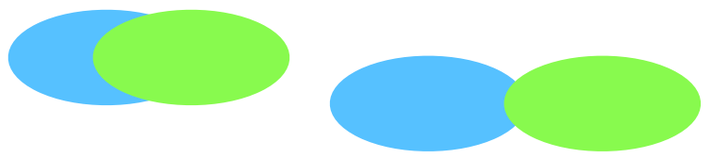


Interaction strength



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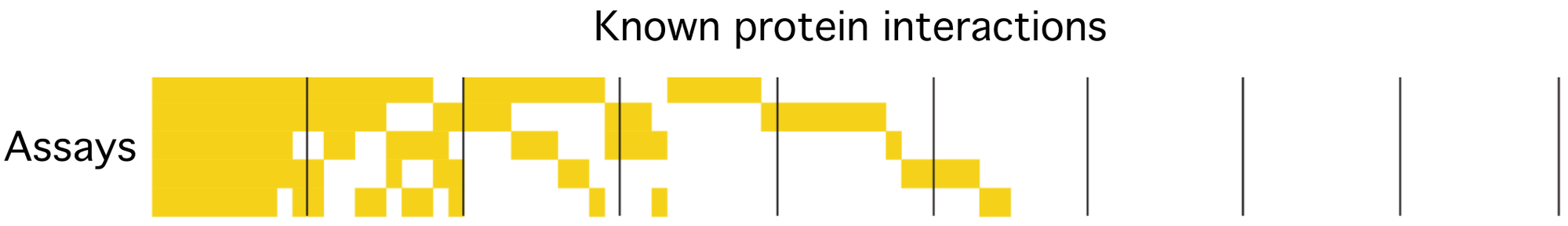

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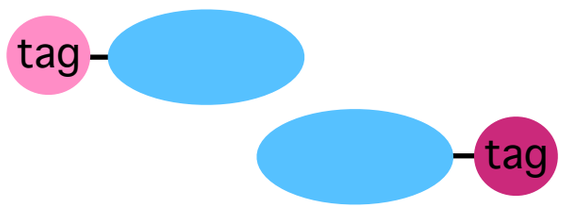

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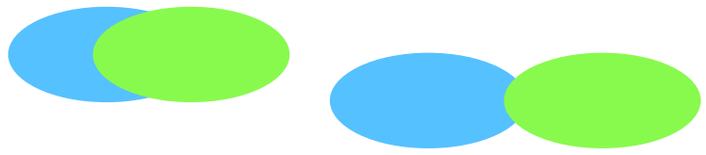
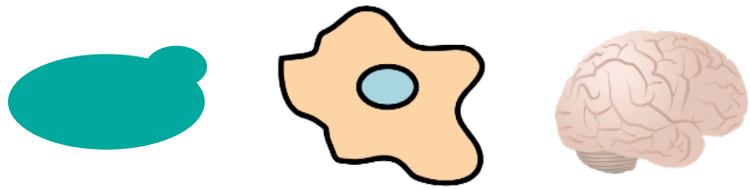


Cellular environment



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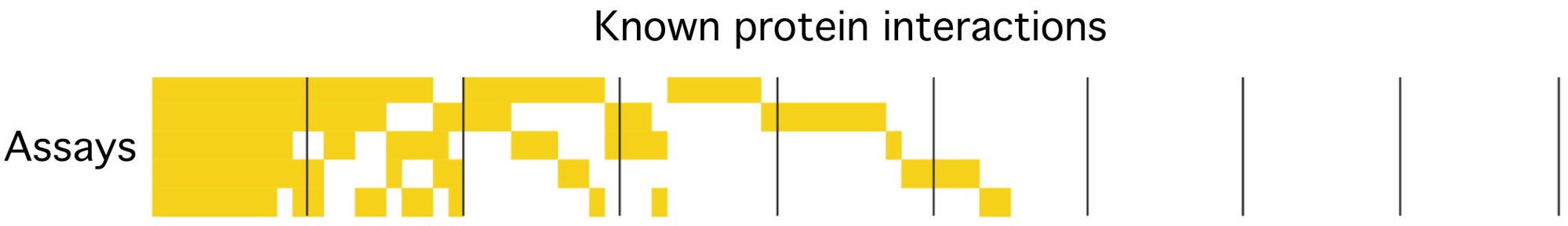

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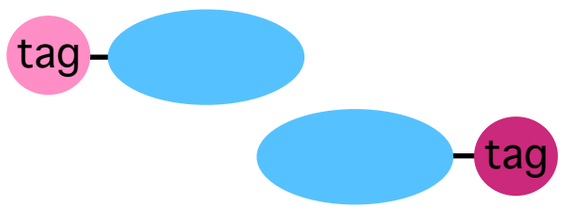

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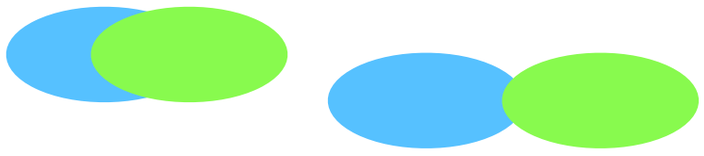

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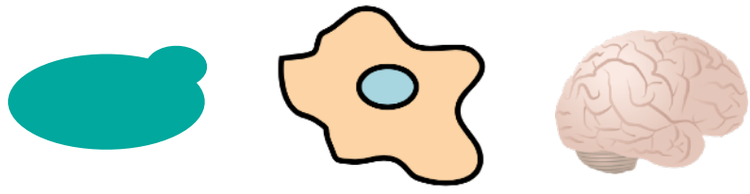
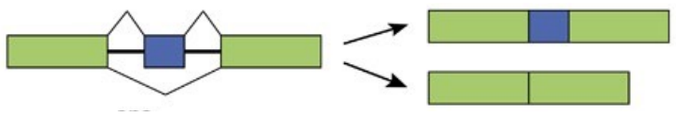


Protein isoforms



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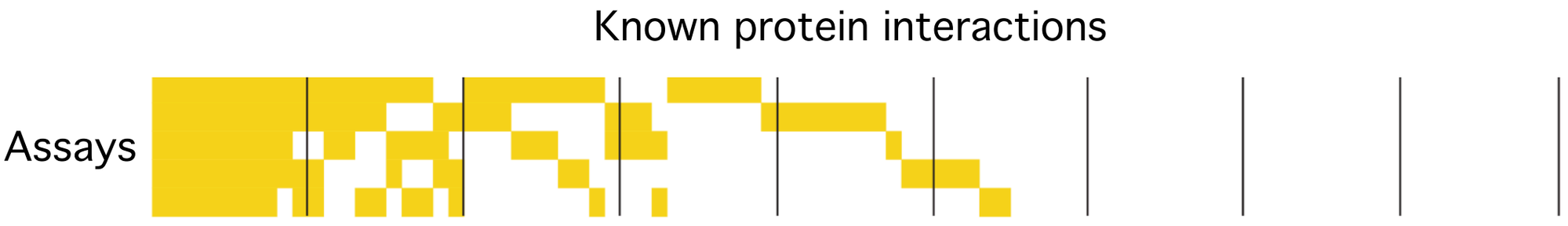

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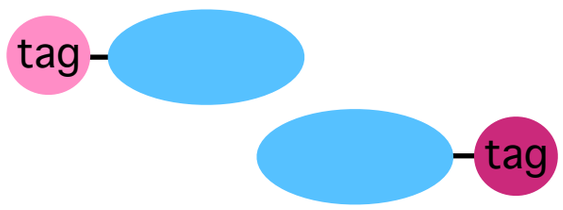

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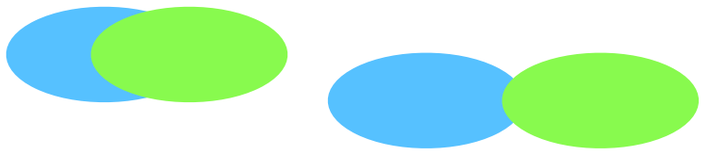

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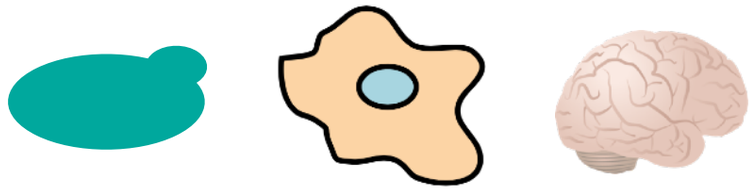

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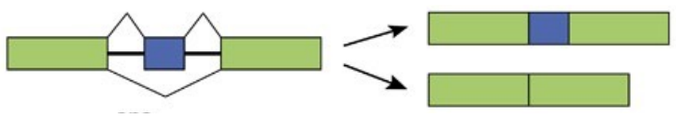
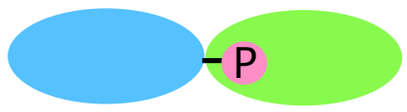


Post-translational modifications



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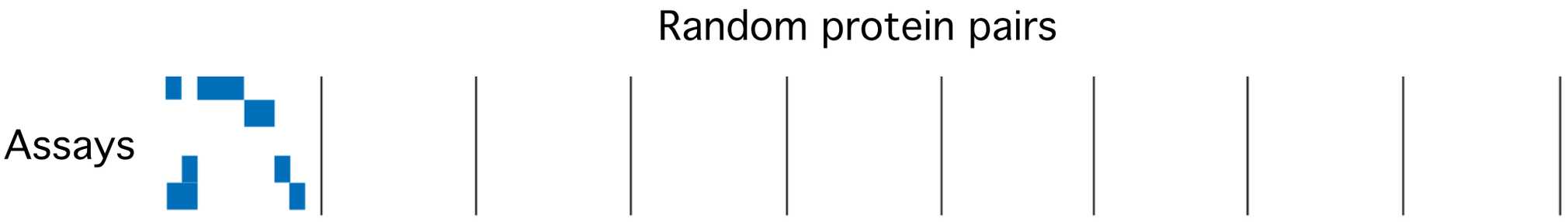

Why would an assay erroneously report a protein interaction?

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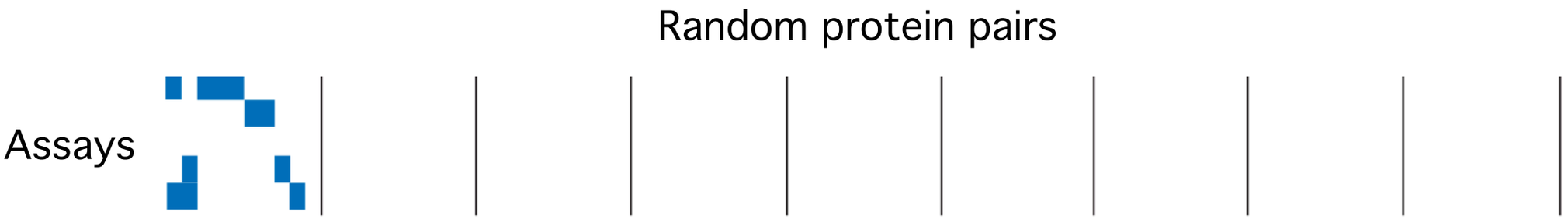

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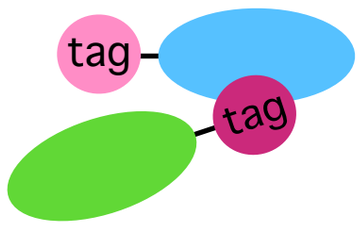

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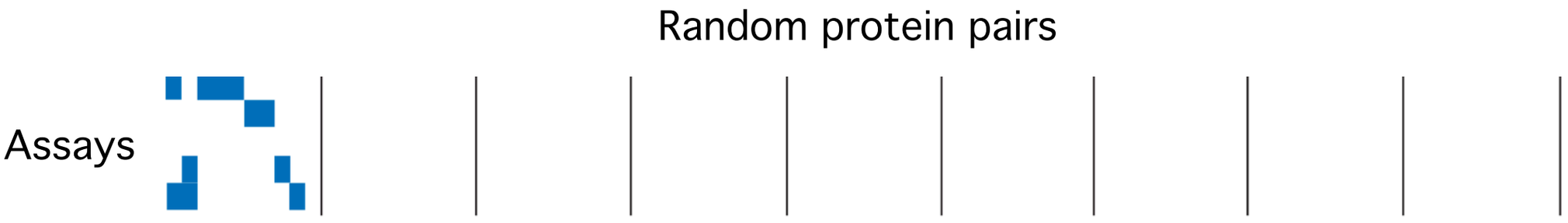

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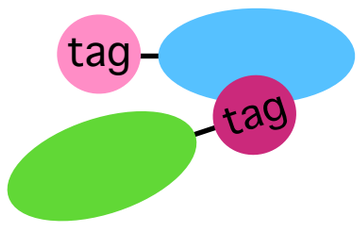

Contamination (AP-MS)

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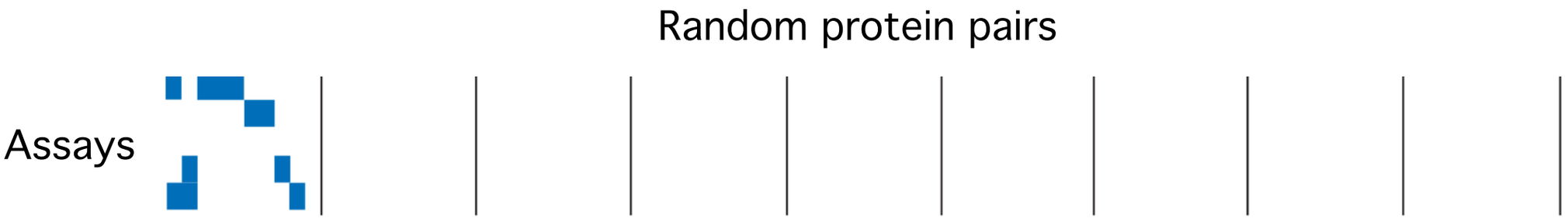

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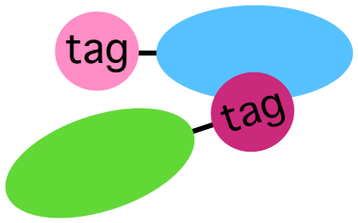
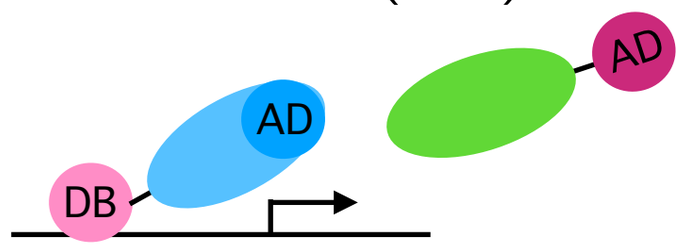


Contamination (AP-MS)

Auto-activation (Y2H)



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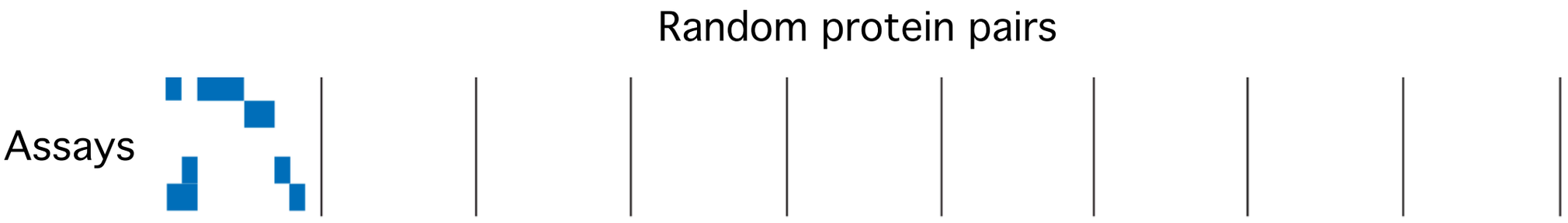

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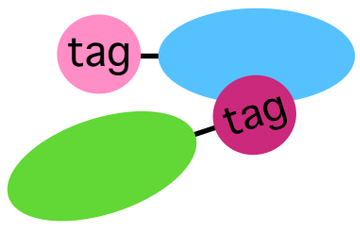

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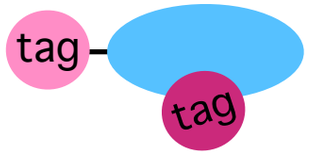

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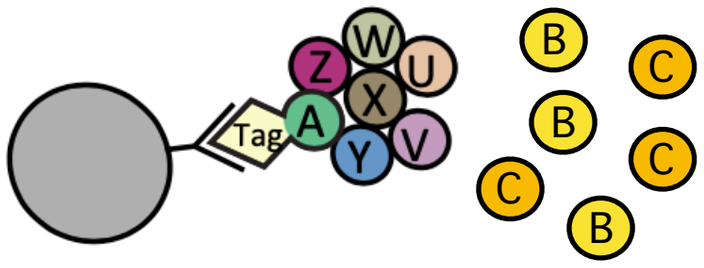

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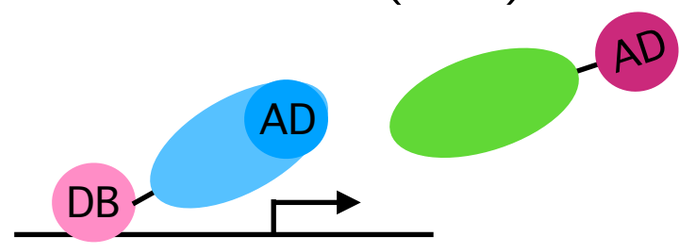

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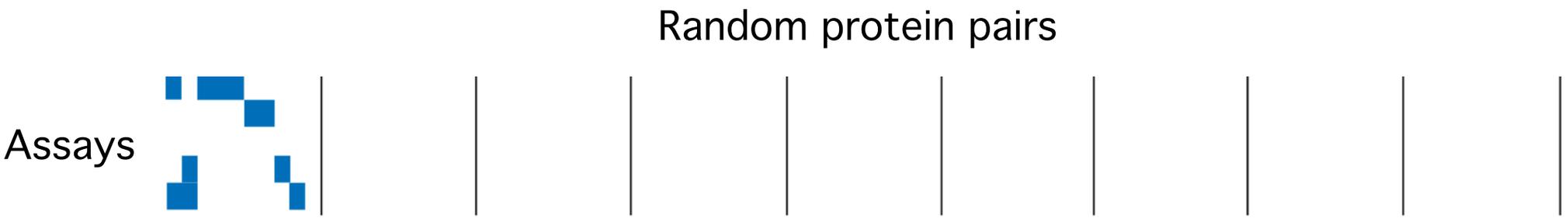
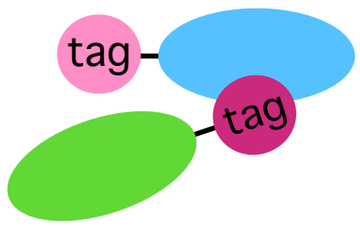
Accuracy of protein interaction assays

Specificity of protein interaction assays

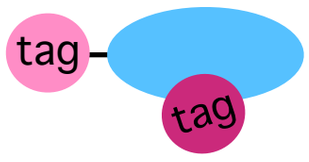


Why would an assay erroneously report a protein interaction?

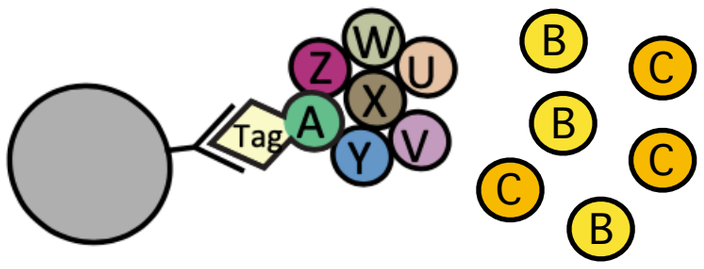
Protein fusions



Control



Contamination (AP-MS)



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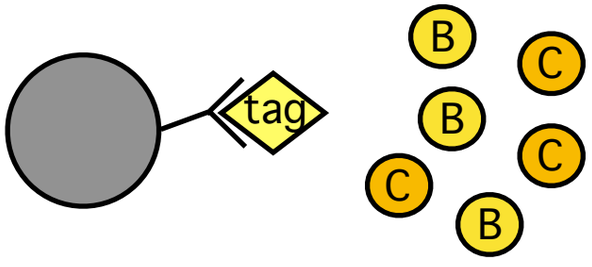
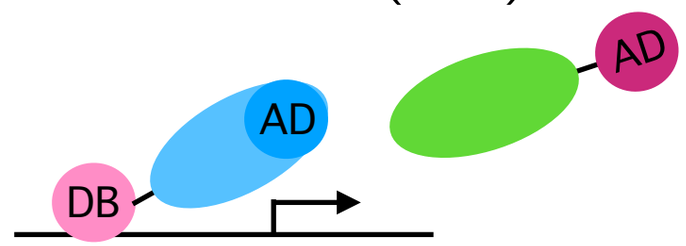


Auto-activation (Y2H)



Braun et al *Nature Methods* 2009

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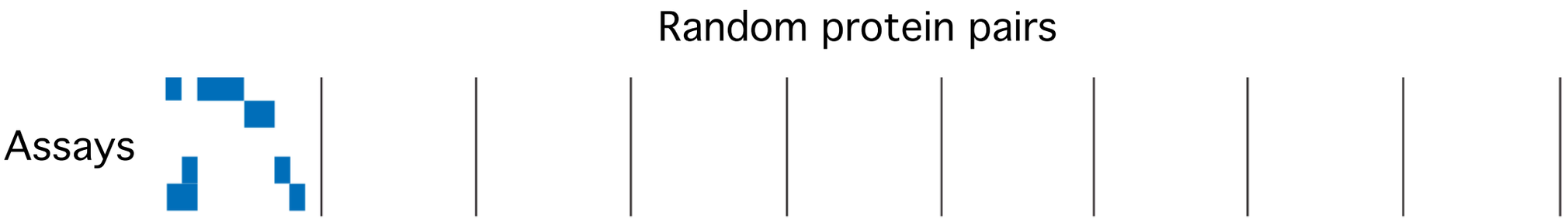

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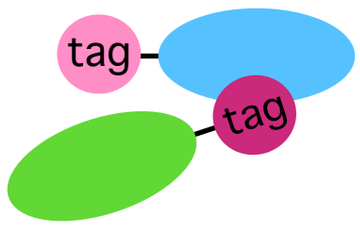

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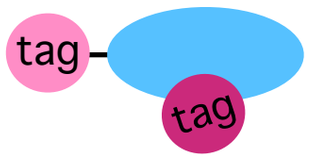

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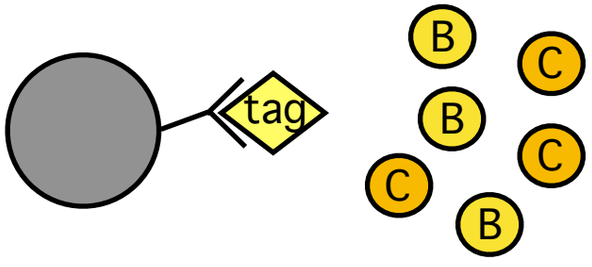

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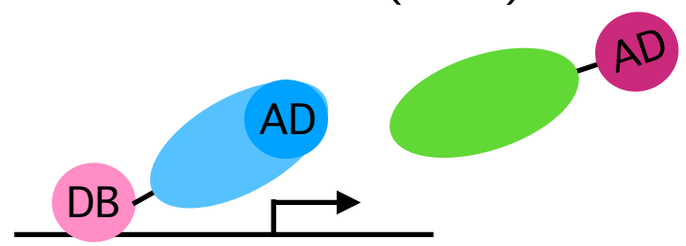
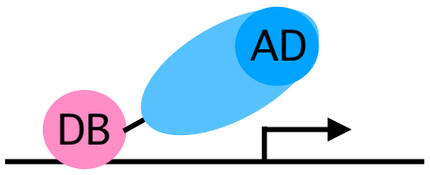


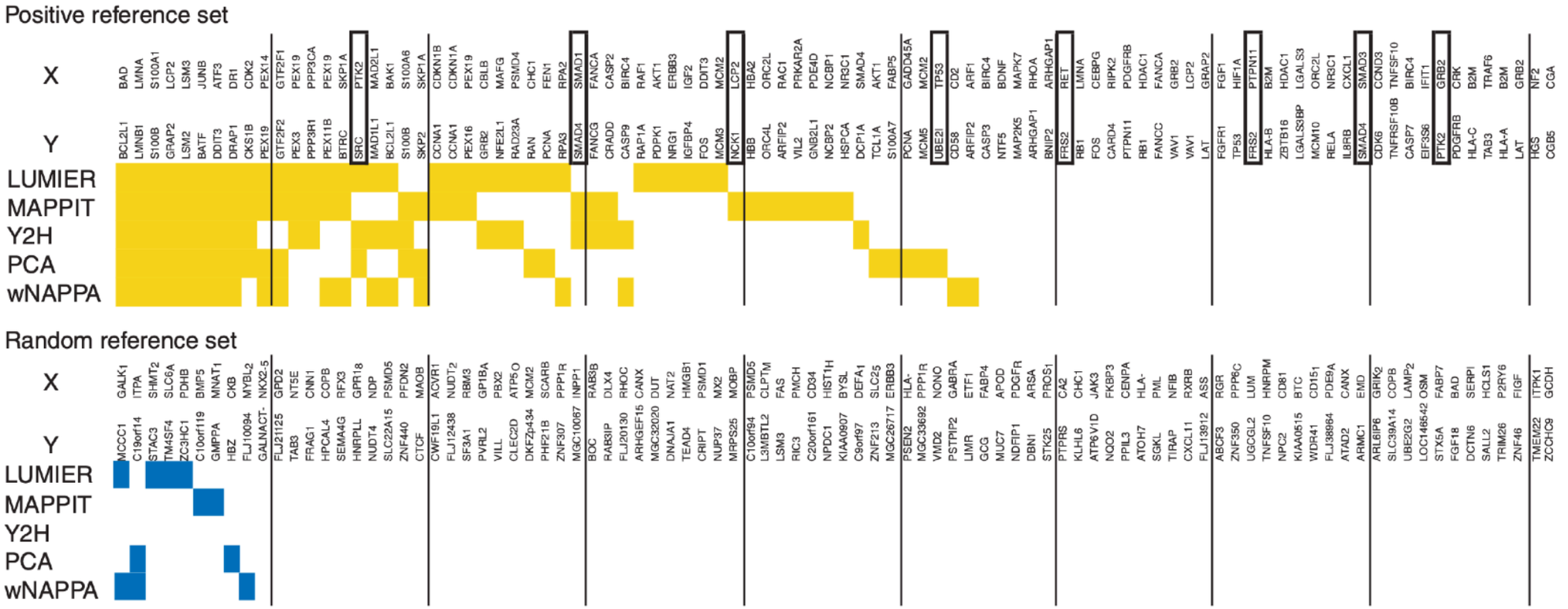
Control



Braun et al *Nature Methods* 2009

Accuracy of protein interaction assays

Correct benchmarking of assays



Braun et al *Nature Methods* 2009, Luck et al *TiBS* 2017

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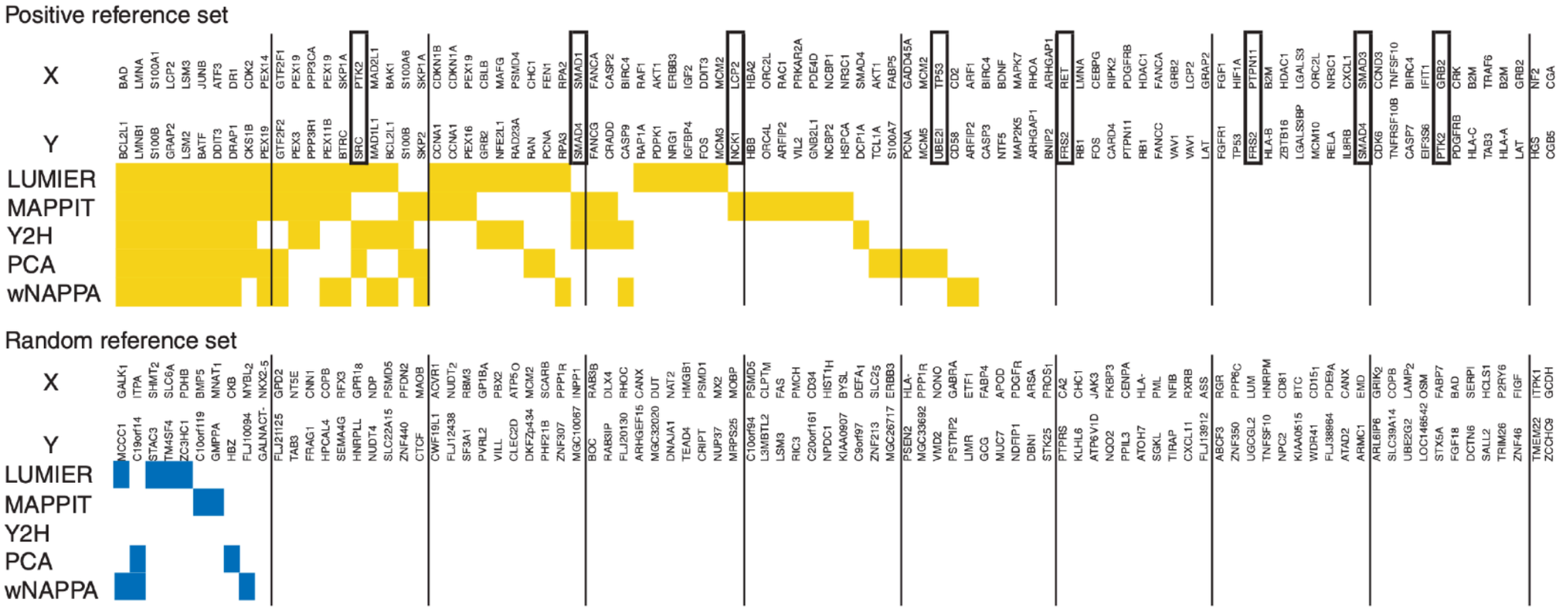
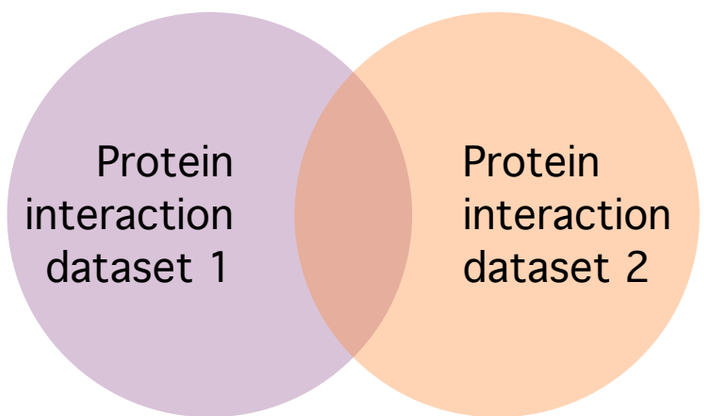


Correct interpretation of protein interaction data

Low overlap



→ Low sensitivity
High specificity

Braun et al *Nature Methods* 2009, Luck et al *TiBS* 2017

Functional relevance of detected protein interactions

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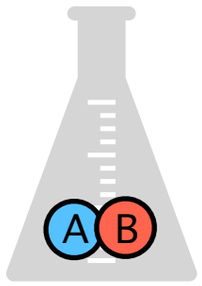
Often artificial context when protein interaction is detected

In vitro



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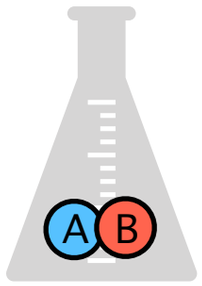
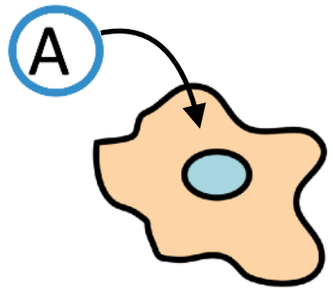


Exogenous expression



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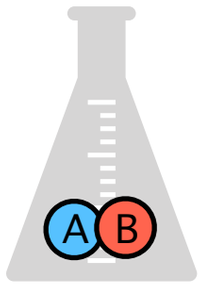

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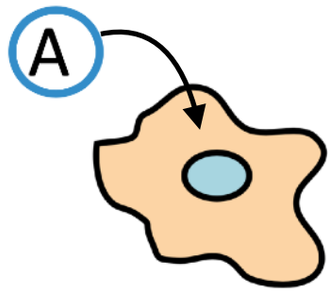
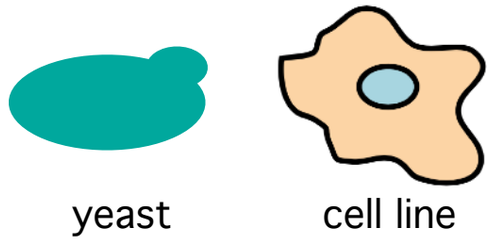


Cellular context



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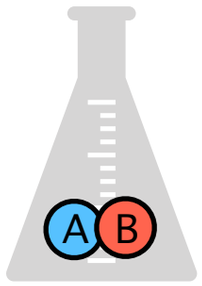

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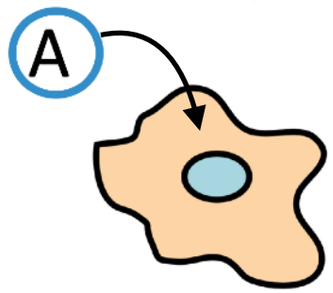

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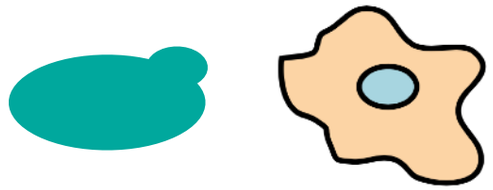
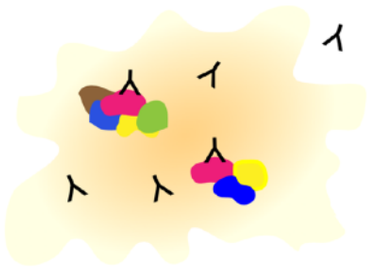


yeast cell line

Cell lysis



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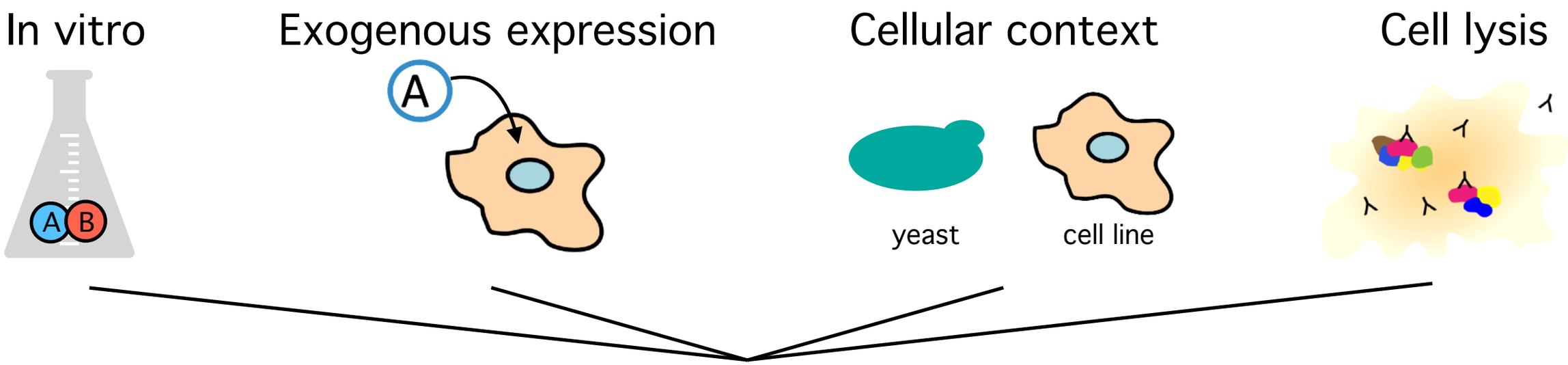

At which cellular context is a detected protein interaction functional?

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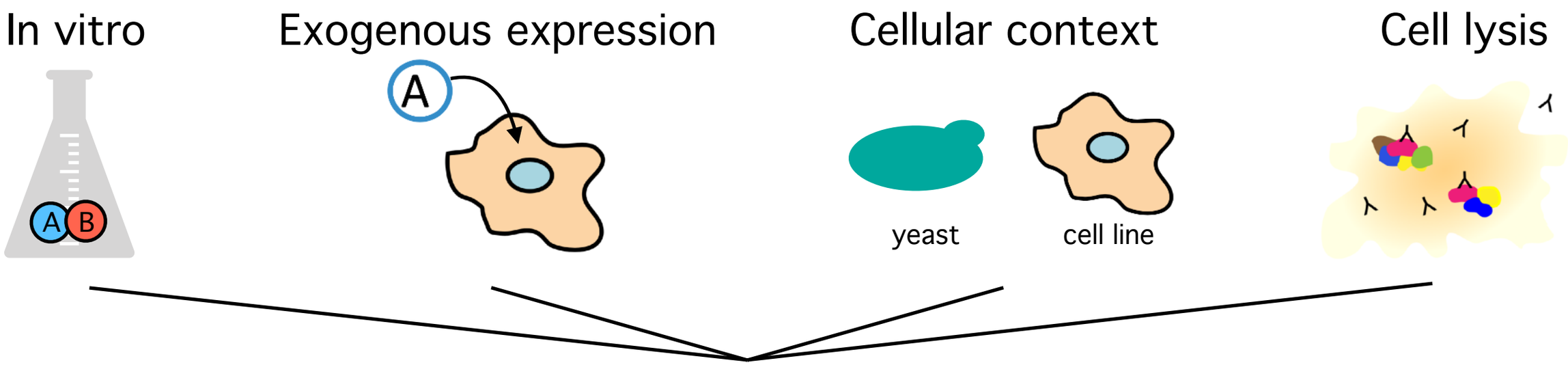

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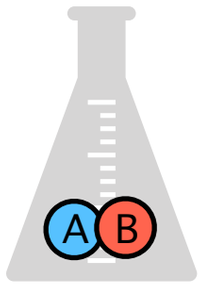

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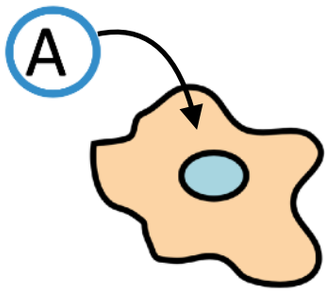

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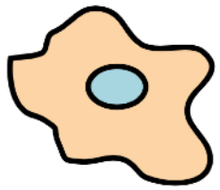

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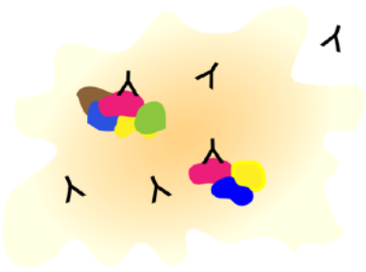

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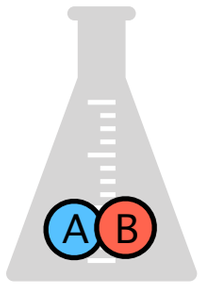

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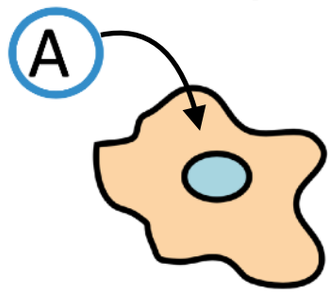

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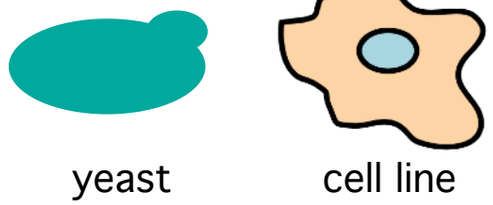

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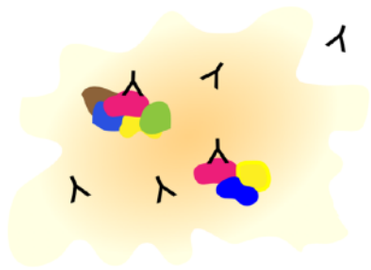

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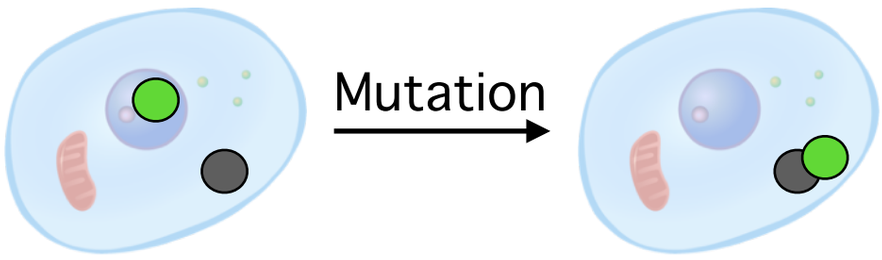

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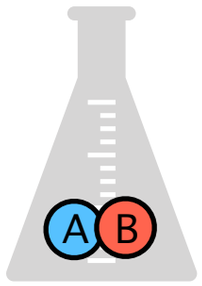

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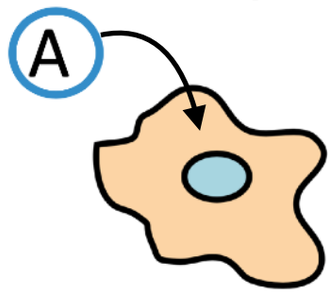

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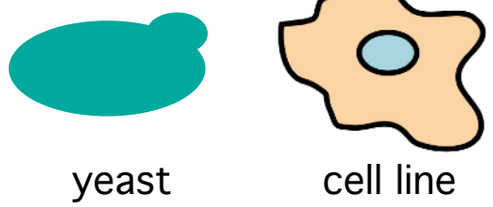

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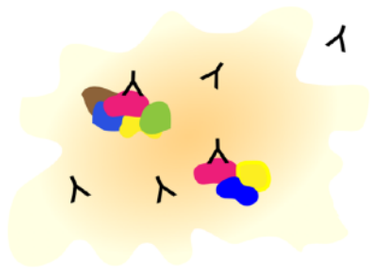

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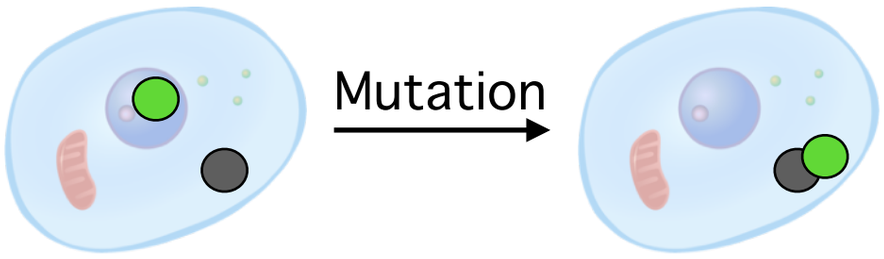

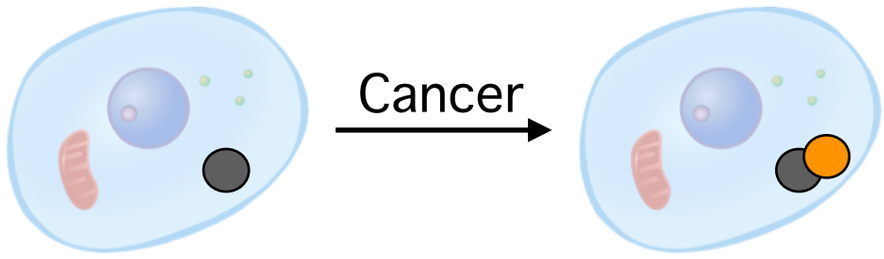

Methods to detected protein interactions

Summary

- interaction strength is a continuum
- most common methods are direct, binary, and co-complex assays
- different methods detect different types of protein interactions
- many interactions remain undetected
- if properly controlled interaction data can be of high quality
- it is difficult to distinguish between functional and non-functional protein interactions